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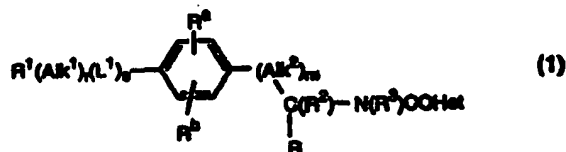


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<p>(21) International Application Number: PCT/GB99/00279</p> <p>(22) International Filing Date: 27 January 1999 (27.01.99)</p> <p>(30) Priority Data: 9801674.4 27 January 1998 (27.01.98) GB 9826669.5 3 December 1998 (03.12.98) GB</p> <p>(71) Applicant (for all designated States except US): CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HEAD, John, Clifford [GB/GB]; 4 Dorchester Close, Maidenhead, Berkshire SL6 6RX (GB). ARCHIBALD, Sarah, Catherine [GB/GB]; 5 College Glen, Maidenhead, Berkshire SL6 6BL (GB). WARRELOW, Graham, John [GB/GB]; Oakside, 4 Wieland Road, Northwood, Middlesex HA6 3QU (GB). PORTER, John, Robert [GB/GB]; 7 Farm Place, Henton, Chinnor, Oxfordshire OX9 4AD (GB).</p> <p>(74) Agent: MERCER, Christopher, Paul; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>

(54) Title: PHENYLALANINE DERIVATIVES USEFUL AS PHARMACEUTICAL AGENTS



(57) Abstract

Phenylalanine derivatives of formula (1) are described, wherein R is a carboxylic acid or a derivative thereof; L¹ is a linker atom or group; Het is an optionally substituted heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of alpha4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

PHENYALANINE DERIVATIVES USEFUL AS PHARMACEUTICAL AGENTS

This invention relates to a series of phenylalanine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. Nature, 346, 425, (1990); Springer, T. A. Cell 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* J. Exp. Med. 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

5 The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al*/ Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al*/ J. Immunol. 157, 4094, (1996)]. A number of
10 monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

15 One particular integrin subgroup of interest involves the $\alpha 4$ chain which can pair with two different beta chains $\beta 1$ and $\beta 7$ [Sonnenberg, A. *ibid*]. The $\alpha 4\beta 1$ pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. $\alpha 4\beta 1$ binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1)
20 frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed
25 that the interaction between $\alpha 4\beta 1$ and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

30 The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like $\alpha 4\beta 1$, binds to VCAM-1 and fibronectin. In addition, $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)].
35 The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important at

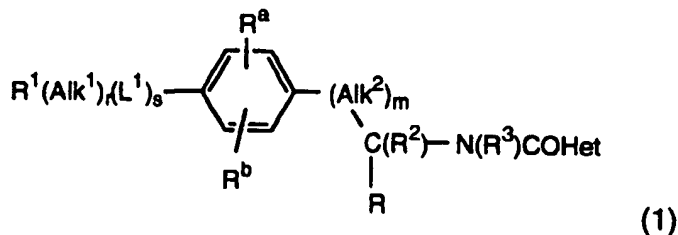
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they
5 bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV,
IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in
VCAM-1 [Humphries, M. J. *et al, ibid*] whilst $\alpha 4\beta 7$ recognises a LDT
sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719,
10 (1996)]. There have been several reports of inhibitors of these interactions
being designed from modifications of these short peptide sequences
[Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N.
Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol.
158, 1710, (1997)]. It has also been reported that a short peptide
15 sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a
contact hypersensitivity reaction in a trinitrochlorobenzene sensitised
mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on
leukocytes their inhibition can be expected to be beneficial in a number of
20 immune or inflammatory disease states. However, because of the
ubiquitous distribution and wide range of functions performed by other
members of the integrin family it is very important to be able to identify
selective inhibitors of the alpha 4 subgroup.

25 We have now found a group of compounds which are potent and selective
inhibitors of $\alpha 4$ integrins. Members of the group are able to inhibit $\alpha 4$
integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ at concentrations at which they
generally have no or minimal inhibitory action on α integrins of other
subgroups. The compounds are thus of use in medicine, for example in
30 the prophylaxis and treatment of immune or inflammatory disorders as
described hereinafter.

Thus according to one aspect of the invention we provide a compound of
formula (1)



wherein

R is a carboxylic acid or a derivative thereof;

- 5 R¹ is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

L¹ is a linker atom or group;

- 10 r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R¹ is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

R^a and R^b, which may be the same or different is each an atom or group

- 15 -L²(CH₂)_pL³(R^c)_q in which L² and L³ is each a covalent bond or a linker atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^c is a hydrogen or halogen atom or a group selected from straight or branched alkyl, -OR^d [where R^d is a hydrogen atom or an optionally substituted straight or branched alkyl group], -SR^d, -NR^dR^e, [where R^e is as just defined for R^d and may be the same or different], -NO₂, -CN, -CO₂R^d, -SO₃H, -SO₂R^d, -OCO₂R^d, -CONR^dR^e, -OCONR^dR^e, -CSNR^dR^e, -COR^d, -N(R^d)COR^e, N(R^d)CSR^e, -SO₂N(R^d)(R^e), -N(R^d)SO₂R^e, -N(R^d)CONR^eR^f [where R^f is a hydrogen atom or an optionally substituted straight or branched alkyl group], -N(R^d)CSNR^eR^f or -N(R^d)SO₂NR^eR^f;

- 25 Alk² is a straight or branched alkylene chain;

m is zero or an integer 1;

R² is a hydrogen atom or a methyl group;

R³ is a hydrogen atom or a straight or branched alkyl group;

Het is an optionally substituted heteroaromatic group;

- 30 and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include $-\text{CO}_2\text{Alk}^4$ and $-\text{CON}(\text{R}^4)_2$ groups as described herein.

When in the compounds of the invention L^1 is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^4)-$ [where R^4 is a hydrogen atom or a straight or branched alkyl group], $-\text{CON}(\text{R}^4)-$, $-\text{OC}(\text{O})\text{N}(\text{R}^4)-$, $-\text{CSN}(\text{R}^4)-$, $-\text{N}(\text{R}^4)\text{CO}-$, $-\text{N}(\text{R}^4)\text{C}(\text{O})\text{O}-$, $-\text{N}(\text{R}^4)\text{CS}-$, $-\text{S}(\text{O})\text{N}(\text{R}^4)-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^4)-$, $-\text{N}(\text{R}^4)\text{S}(\text{O})-$, $-\text{N}(\text{R}^4)\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^4)\text{CON}(\text{R}^4)-$, $-\text{N}(\text{R}^4)\text{CSN}(\text{R}^4)-$, $-\text{N}(\text{R}^4)\text{SON}(\text{R}^4)-$ or $-\text{N}(\text{R}^4)\text{SO}_2\text{N}(\text{R}^4)-$ groups. Where the linker group contains two R^4 substituents, these may be the same or different.

Alk^2 in the compounds of the invention may be for example a straight or branched C_{1-3} alkylene chain. Particular examples include $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$ and $-(\text{CH}_2)_2-$.

When R^3 and/or R^4 in the compounds of formula (1) is a straight or branched alkyl group it may be a straight or branched C_{1-6} alkyl group, e.g. a C_{1-3} alkyl group such as a methyl or ethyl group.

When Alk^1 in compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl chains.

Heteroaliphatic chains represented by Alk^1 include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^4 where L^4 is as defined above for L^1 when L^1 is a linker atom or group. Each L^4 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to the atom or group R^1 .

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-(\text{CH}_2)_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_3\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_4\text{CH}_2-$, $-(\text{CH}_2)_5\text{CH}_2-$, $-\text{CHCH}-$, $-\text{CHCHCH}_2-$, $-\text{CH}_2\text{CHCH}-$, $-\text{CHCHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CHCHCH}_2-$, $-(\text{CH}_2)_2\text{CHCH}-$, $-\text{CC}-$, $-\text{CCCH}_2-$, $-\text{CH}_2\text{CC}-$, $-\text{CCCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CCCH}_2-$, or $-(\text{CH}_2)_2\text{CC}-$ chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L^4 to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted $-\text{L}^4\text{CH}_2-$, $-\text{CH}_2\text{L}^4\text{CH}_2-$, $-\text{L}^4(\text{CH}_2)_2-$, $-\text{CH}_2\text{L}^4(\text{CH}_2)_2-$, $-(\text{CH}_2)_2\text{L}^4\text{CH}_2-$, $-\text{L}^4(\text{CH}_2)_3-$ and $-(\text{CH}_2)_2\text{L}^4(\text{CH}_2)_2-$ chains. The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6} alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6} alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-\text{NHR}^4$ and $-\text{N}(\text{R}^4)_2$ groups where R^4 is a straight or branched alkyl group as defined above. Where two R^4 groups are present these may be the same or different. Particular examples of substituted chains represented by Alk^1 include those specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type $-\text{CH}(\text{CF}_3)-$, $-\text{C}(\text{CF}_3)_2-$, $-\text{CH}_2\text{CH}(\text{CF}_3)-$, $-\text{CH}_2\text{C}(\text{CF}_3)_2-$, $-\text{CH}(\text{CF}_3)-$ and $-\text{C}(\text{CF}_3)_2\text{CH}_2-$.

Alkoxy groups represented by R^1 in compounds of the invention include straight or branched C_{1-6} alkoxy groups such as methoxy and ethoxy groups.

When R¹ is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C₃₋₁₀ cycloaliphatic group. Particular examples include optionally substituted C₃₋₁₀cycloalkyl, e.g. C₃₋₇cycloalkyl, C₃₋₁₀cycloalkenyl e.g. C₃₋₇cycloalkenyl or C₃₋₁₀cycloalkynyl e.g. C₃₋₇cycloalkynyl groups.

Optionally substituted heterocycloaliphatic groups represented by R¹ include the optionally substituted cycloaliphatic groups just described for R¹ but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups L² as just defined.

Optionally substituted polycycloaliphatic groups represented by R¹ include optionally substituted C₇₋₁₀ bi- or tricycloalkyl or C₇₋₁₀bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by R¹ include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L² atoms or groups.

Particular examples of R¹ cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, pyrrolidine, e.g. 2- or 3-pyrrolidinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolyl, e.g. 2-imidazolyl, imidazolidinyl, pyrazolyl, e.g. 2-pyrazolyl, pyrazolidinyl, thiazolyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

The optional substituents which may be present on the R¹ cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups include one, two, three or more substituents represented by R⁵ in which R⁵ is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, haloC₁₋₆alkyl, e.g.

halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, hydroxyl, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C₁₋₆alkylthio e.g. methylthio or ethylthio, -N(R⁴)₂, -CN, -CO₂R⁴, -NO₂, -CON(R⁴)₂,
 5 -CSN(R⁴)₂, -COR⁴, -CSN(R⁴)₂, -N(R⁴)COR⁴, -N(R⁴)CSR⁴, -SO₂N(R⁴)₂,
 -N(R⁴)SO₂R⁴, -N(R⁴)CON(R⁴)₂, -N(R⁴)CSN(R⁴) and -N(R⁴)SO₂N(R⁴)₂ groups. In these substituents the group R⁴ when present is a hydrogen atom or a straight or branched alkyl group as defined above. Where more than one R⁴ group is present in a substituent each group may be the same
 10 or different. The substituent may be present on any available carbon atom or where appropriate any nitrogen atom, in the R¹ group.

In the compounds of formula (1), optionally substituted aromatic groups represented by the group R¹ include for example monocyclic or bicyclic
 15 fused ring C₆₋₁₂ aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups, optionally substituted by one, two, three or more -L²(CH₂)_pL³(R^c)_q atoms or groups, where L², L³, p and q are as previously defined and R^c is as previously defined but is other than a hydrogen atom when L² and L³ is each a covalent bond and p
 20 is zero.

Optionally substituted heteroaromatic groups, represented by the group R¹ or Het in compounds of formula (1) include for example optionally substituted C₁₋₉ heteroaromatic groups containing for example one, two,
 25 three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms
 30 selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

35 Particular examples of heteroaromatic groups of these types include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆imidazolyl,

oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazol, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]-
 5 benzofuryl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinoliny, isoquinoliny, tetrazolyl, 5,6,7,8-tetrahydroquinoliny, 5,6,7,8-tetrahydroisoquinoliny, and imidyl,
 10 e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on R¹ heteroaromatic groups include one, two, three or more -L²(CH₂)_pL³(R^c)_q atoms on groups as just
 15 defined.

Examples of the substituents represented by R^a and R^b in compounds of formula (1) and which may be present on aromatic or heteroaromatic groups represented by R¹ include atoms or groups -L²(CH₂)_pL^{Rc},
 20 -L²(CH₂)_pR^c, -L²R^c, -(CH₂)_pR^c and -R^c wherein L², (CH₂)_p, L and R^c are as defined above. Particular examples of such substituents include -L²CH₂L²R^c, -L²CH(CH₃)L³R^c, -L²(CH₂)₂L³R^c, -2CH₂R^c, -L²CH(CH₃)R^c, -L²(CH₂)₂R^c, -CH₂R^c, -CH(CH₃)R^c and -(CH₂)₂R^c groups.

25 Thus each of R^a and R^b and, where present, substituents on R¹ aromatic or heteroaromatic groups in compounds of the invention may be for example selected from a hydrogen atom, a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, or a C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C₁₋₆alkylamino, e.g. methylamino or
 30 ethylamino, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or -C(OH)(CF₃)₂, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, haloC₁₋₆alkyl, e.g. -CF₃,
 35 -CHF₂, CH₂F, haloC₁₋₆alkoxy, e.g. -OCF₃, -OCHF₂, -OCH₂F, C₁₋₆alkyl-amino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, .g.

- aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂R¹², C₁₋₆alkanoyl e.g. acetyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonylmethylamino, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidomethylamino, C₁₋

alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino group.

- Optional substituents present on the heteroaromatic groups represented by Het include one, two, three or more substituents, each selected from an atom or group R^6 in which R^6 is $-R^{6a}$ or $-\text{Alk}^3(R^{6a})_m$, where R^{6a} is a halogen atom, or an amino ($-\text{NH}_2$), substituted amino, nitro, cyano, amidino, hydroxyl ($-\text{OH}$), substituted hydroxyl, formyl, carboxyl ($-\text{CO}_2\text{H}$), esterified carboxyl, thiol ($-\text{SH}$), substituted thiol, $-\text{COR}^7$ [where R^7 is an $-\text{Alk}^3(R^{6a})_m$, aryl or heteroaryl group], $-\text{CSR}^7$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{R}^7$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHR}^7$, $-\text{SO}_2\text{N}(\text{R}^7)_2$, $-\text{CONH}_2$, $-\text{CSNH}_2$, $-\text{CONHR}^7$, $-\text{CSNHR}^7$, $-\text{CON}(\text{R}^7)_2$, $-\text{CSN}(\text{R}^7)_2$, $-\text{N}(\text{R}^4)\text{SO}_2\text{R}^7$, $-\text{N}(\text{SO}_2\text{R}^7)_2$, $-\text{NH}(\text{R}^4)\text{SO}_2\text{NH}_2$, $-\text{N}(\text{R}^4)\text{SO}_2\text{NHR}^7$, $-\text{N}(\text{R}^4)\text{SO}_2\text{N}(\text{R}^7)_2$, $-\text{N}(\text{R}^4)\text{COR}^7$, $-\text{N}(\text{R}^4)\text{CON}(\text{R}^7)_2$, $-\text{N}(\text{R}^4)\text{CSN}(\text{R}^7)_2$, $-\text{N}(\text{R}^4)\text{CSR}^7$, $-\text{N}(\text{R}^4)\text{C}(\text{O})\text{OR}^7$, $-\text{SO}_2\text{NH}^{\text{st}1}$ [where $-\text{NHet}^1$ is an optionally substituted C_{5-7} cyclicamino group optionally containing one or more other $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{N}(\text{R}^4)-$, $-\text{C}(\text{O})-$ or $-\text{C}(\text{S})-$ groups], $-\text{CONHet}^1$, $-\text{CSNHet}^1$, $-\text{N}(\text{R}^4)\text{SO}_2\text{NHet}^1$, $-\text{N}(\text{R}^4)\text{CONHet}^1$, $-\text{N}(\text{R}^4)\text{CSNHet}^1$, $-\text{SO}_2\text{N}(\text{R}^4)\text{Het}^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7} carbocyclic group optionally containing one or more $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{N}(\text{R}^4)-$, $-\text{C}(\text{O})-$ or $-\text{C}(\text{S})-$ groups], $-\text{CON}(\text{R}^4)\text{Het}^2$, $-\text{CSN}(\text{R}^4)\text{Het}^2$, $-\text{N}(\text{R}^4)\text{CON}(\text{R}^4)\text{Het}^2$, $-\text{N}(\text{R}^4)\text{CSN}(\text{R}^4)\text{Het}^2$, aryl or heteroaryl group; Alk^3 is a straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{S}(\text{O})_n$ [where n is an integer 1 or 2] or $-\text{N}(\text{R}^8)-$ groups [where R^8 is a hydrogen atom or C_{1-6} alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^4 or R^7 groups are present in one of the above substituents, the R^4 or R^7 groups may be the same or different.
- When in the group $-\text{Alk}^3(\text{R}^{6a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{6a} may be present on any suitable carbon atom in $-\text{Alk}^3$. Where more than one R^{6a} substituent is present these may be the same or different and may be present on the same or different atom in $-\text{Alk}^3$. Clearly, when m is zero and no substituent R^{6a} is present the alkyl, alkenyl or alkynyl chain represented by Alk^3 comprises an alkyl, alkenyl or alkynyl group.

When R^{6a} is a substituted amino group it may be for example a group $-NHR^7$ [where R^7 is as defined above] or a group $-N(R^7)_2$ wherein each R^7 group is the same or different.

5

When R^{6a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{6a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^7$ or a $-SR^7$ or $-SC(=NH)NH_2$ group respectively.

10

Esterified carboxyl groups represented by the group R^{6a} include groups of formula $-CO_2Alk^4$ wherein Alk^4 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^4 group include R^{6a} substituents described above.

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When Alk^3 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butyneylene or 3-butyneylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R^8)- groups.

30

Aryl or heteroaryl groups represented by the groups R^{6a} or R^7 include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the groups R^1 and Het.

35

The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero, e.g. nitrogen atom as appropriate.

- 5 When -NHet¹ or -Het² forms part of a substituent R⁶ each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹
 10 or -Het² include those R⁵ substituents described above.

Particularly useful atoms or groups represented by R⁶ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrrolyl,
 15 furyl, thiazolyl, or thienyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-
 20 hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyloxy, phenylthio or pyridylthio, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g.
 25 dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as
 30 phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁴ [where Alk⁴ is as defined above], C₁₋₆alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methyl-
 35 sulphonyl, optionally substituted phenylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or

- ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylamino-sulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, benzylthio, pyridylmethylthio or thiazolylmethylthio groups.
- In the above groups of particularly useful R⁶ substituents, the reference to optional substitution is intended to relate primarily to the aromatic or

heteroaromatic portions of the groups described. Thus for example such groups may be optionally mono-, di- or tri-substituted by those particular atoms or groups described above for each of R^a and R^b .

- 5 Where desired, two R^6 substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6} alkylenedioxy group such as methylenedioxy or ethylenedioxy.

- 10 It will be appreciated that where two or more R^6 substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the heteroaromatic group represented by Het.

- 15 The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

- 20 Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates,
25 succinates, lactates, oxalates, tartrates and benzoates.

- Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine,
30 piperidine, dimethylamine or diethylamine salts.

- Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

35

R in compounds of the invention is preferably a $-CO_2H$ group.

When present, the aliphatic chain represented by Alk¹ in compounds of the invention is preferably a -CH₂- chain.

- 5 Alk² in compounds of formula (1) is preferably a -CH₂- chain and m is preferably an integer 1. In compounds of this type, the carbon atom to which Alk² and R are attached forms a chiral centre and is preferably in the L configuration.
- 10 R² in compounds of formula (1) is preferably a hydrogen atom.

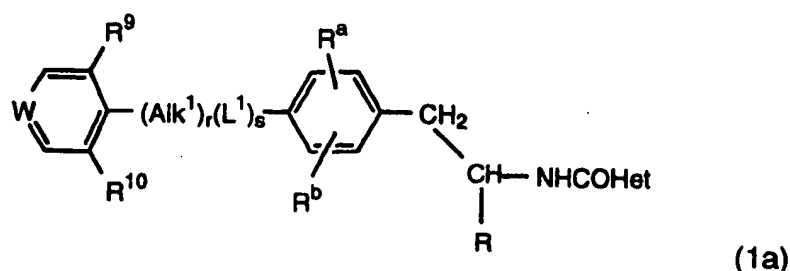
R³ in compounds of the invention is preferably a hydrogen atom.

- 15 In general in compounds of the invention -(Alk¹)_r(L¹)_s is preferably -CH₂O-, -SO₂NH-, -C(O)O- or -CON(R⁴)- and is especially -CONH-.

- 20 In general in compounds of the invention the group R¹ is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substituted phenyl, pyridyl or pyrimidinyl groups, particularly those in which the substituent when present is an atom or group -L²(CH₂)_pL³(R^c)_q as described above. Each substituent may be present on any available ring carbon or nitrogen atom.

- 25 The heteroaromatic group represented by Het in compounds of formula (1) is preferably an optionally substituted C₃₋₅ monocyclic heteroaromatic group containing one, two or three heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly useful groups of this type include optionally substituted pyrrolyl and pyridyl groups. Especially useful heteroaromatic groups represented by Het include optionally substituted 3- or 4-pyridyl groups, particularly 2-monosubstituted 3- or 4-pyridyl or 2,6-disubstituted 3- or 4-pyridyl groups. In these, and in general in the group Het, the optional substituent when present is preferably an atom or group R⁶ as defined above.

- 35 A particularly useful class of compounds according to the invention has the formula (1a)



5 wherein -W= is -CH= or -N=, R^9 and R^{10} , which may be the same or different is each a $-L^2(CH_2)_pL^3(R^c)_q$ atom or group as generally and particularly defined above, and Alk^1 , r , L^1 , s , R^a , R^b , R and Het are as generally and particularly defined above, and the salts, solvates, hydrates and N-oxides thereof.

10 It will be appreciated that the various preferences stated above in relation to groups present in compounds of formula (1) apply equally to the same groups when present in compounds of formula (1).

15 Additionally, in the compounds of formula (1a) $-(Alk^1)_r(L^1)_s-$ is preferably a $-CH_2O$ or $-CON(R^4)-$ group and is especially a $-CONH-$ group. Het is preferably an optionally substituted pyrrolyl or especially an optionally substituted pyridyl group.

20 Particularly useful compounds of formula (1a) are those wherein Het is a 2-monosubstituted 3- or 4-pyridyl group or a 2,6-disubstituted 3- or 4-pyridyl group.

25 One of R^9 or R^{10} in compounds of formula (1a) may be for example a hydrogen atom and the other a substituent $L^2(CH_2)_pL^3(R^c)_q$ in which R^c is not a covalent bond and p is zero, but preferably each of R^9 and R^{10} is a substituent $-L^2(CH_2)_pL^3(R^c)_q$ where R^c is as just defined. Particularly useful R^9 or R^{10} substituents include a hydrogen atom or halogen atom, especially fluorine or chlorine atoms, or a methyl, ethyl, methoxy, ethoxy, $-CF_3$, $-OH$, $-CN$, $-NO_2$, $-NH_2$, $-NHCH_2$, $-N(CH_3)_2$, $-COCH_3$, $-SCH_3$, $-CO_2H$ or $-CO_2CH_3$ group.

30

Particularly useful compounds according to the invention include the following:

- 2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine;
- 5 2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine;
- N*-(3,5-Dichloro-4-picolyl)-*N'*-(3,5-dichloro-4-picolyl)-L-4-amino-phenylalanine;
- N*-(2-Chloronicotinoyl)-*N'*-(3,5-dichloro-4-picolyl)-L-4-amino-phenylalanine;
- 10 *O*-(2,6-dichlorobenzyl)-*N*-(4-acetyl-1,2,5-trimethyl-3-pyrrolyl)-L-tyrosine;
- (*N'*-3,5-Dichloroisonicotinoyl)-*N*-{[3-pyridinylmethyl]thio}isonicotinoyl)-L-4-aminophenylalanine;
- N*-(4-Acetyl-1,2,5-trimethyl-1*H*-pyrrole-3-carbonyl)-*N'*-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine; and the salts, solvates, hydrates and N-
- 15 oxides thereof.

Compounds according to the invention are potent and selective inhibitors of α_4 integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the

20 Examples hereinafter. In particular compounds of the invention, such as the compounds of formula (1a) herein, the compounds are advantageously selective $\alpha_4\beta_1$ inhibitors.

The compounds are of use in modulating cell adhesion and in particular

25 are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders.

30 Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

35

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

10

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

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25

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

30

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule

35

or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively,
5 the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting
10 formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the
15 form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

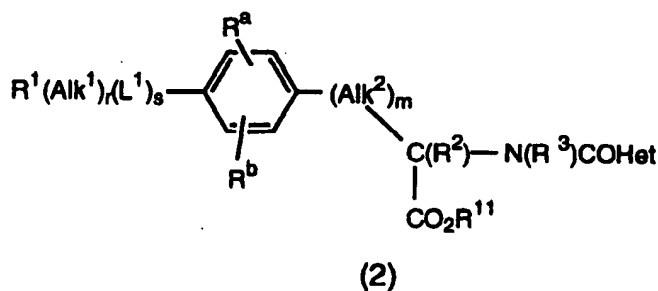
20 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

25 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal
30 administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

35 The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the

Examples hereinafter. In the following process description, the symbols R, R¹-R³, R^a, R^b, L¹, Alk¹, Alk², m, r, s and Het wh n used in the formulae depicted are to be understood to represent thos groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

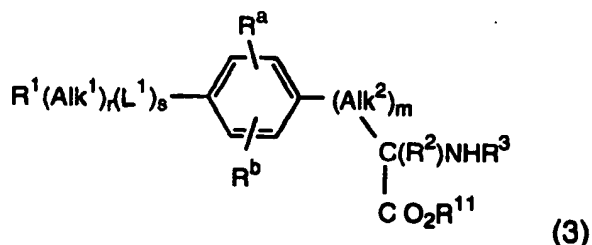
Thus according to a further aspect of the invention, a compound of formula (1) may be obtained by hydrolysis of an ester of formula (2):



where R¹¹ is an alkyl group.

The hydrolysis may be performed using either an acid or a base depending on the nature of R¹¹, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (2) may be prepared by coupling an amine of formula (3):



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(where R¹¹ is as just described) or a salt thereof with an acid of formula (4):



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or an active derivative thereof.

Active derivatives of acids of formula (4) include anhydrides, esters and halides. Particular esters include pentafluorophenyl or succinyl esters.

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The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethylaminopyridine, or a cyclic amine, such as N-methylmorpholine.

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Where an acid of formula (4) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate,

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for example ethylchloroformate, prior to reaction with the amine of formula (3).

Intermediates of formulae (2), (3) and (4), or compounds of formula (1),
 5 may be manipulated to introduce substituents to aromatic or heteroaromatic groups or modify existing substituents in groups of these types. Typically, such manipulation may involve standard substitution approaches employing for example alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation
 10 or coupling reactions. Alternatively, existing substituents may be modified for example by oxidation, reduction or cleavage reactions. Particular examples of such reactions are given below. Where these are described in relation to the generation of the group $R^1(Alk^1)_r(L^1)_s$ -, it will be appreciated that each reaction may also be used to introduce or modify R^5
 15 and/or R^6 substituents as appropriate.

Thus in one example, a compound wherein $R^1(Alk^1)_r(L^1)_s$ - is a $-L^1H$ group may be alkylated, arylated or heteroarylated using a reagent $R^1(Alk^1)_rX$ in which R^1 is other than a hydrogen atom and X is a leaving atom or group
 20 such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a
 25 carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

30 In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group is a hydrogen atom may be functionalised by acylation or thioacylation, for example by reaction with a reagent $R^1(Alk^1)_rL^1X$ [wherein L^1 is a $-C(O)-$, $C(S)-$, $-N(R^4)C(O)-$ or $N(R^4)C(S)-$ group], in the presence of a base, such
 35 as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g.

dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature, or by reaction with $R^1(Alk^1)_rCO_2H$, $R^1(Alk^1)_4COSH$ or an activated derivative thereof, for example as described above for the preparation of esters of formula (2).

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In a further example a compound may be obtained by sulphonylation of a compound where $R^1(Alk^1)_r(L^1)_s$ is an $-OH$ group by reaction with a reagent $R^1(Alk^1)_rL^1Hal$ [in which L^1 is $-S(O)-$ or $-SO_2-$ and Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

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In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group, may be coupled with a reagent R^1OH (where R^1 is other than a hydrogen atom) or R^1Alk^1OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate to yield a compound containing a $R^1(Alk^1)_rO-$ group.

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In a further example, ester groups $-CO_2R^4$ or $-CO_2Alk^4$ in compounds of formula (1) may be converted to the corresponding acid $[-CO_2H]$ by acid- or base-catalysed hydrolysis depending on the nature of the group R^4 or Alk^4 . Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

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In a second example, $-OR^7$ [where R^7 represents an alkyl group such as methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol $-OH$ by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around $-78^\circ C$.

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Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding -OCH₂R⁷ group (where R⁷ is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [-CO₂Alk⁴ or CO₂R⁴] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

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In another example, alcohol -OH groups in compounds of formula (1) may be converted to a corresponding -OR³ group by coupling with a reagent R⁷OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

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Aminosulphonylamino [-NHSO₂NH₂] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

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In a further example amine (-NH₂) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

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In a further example, amine [-NH₂] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

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In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen

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in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, .g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

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Aromatic halogen substituents in compounds of the invention may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

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15 In another example, sulphur atoms in compounds of the invention, for example when present in the linker group L¹ may be oxidised to the corresponding sulfoxide using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

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Intermediates of formulae (3) and (4), R¹(Alk¹)_rX, R¹(Alk¹)_rL¹X, R¹(Alk¹)_rCO₂H, R¹OH and R¹Alk¹OH are either known compounds or may be prepared from known starting materials by use of analogous processes to those used for the preparation of the known compounds and/or by treating known compounds by one or more of the alkylation, acylation and other manipulations described herein, such as particularly described for the preparation of the Intermediates in the exemplification selection hereinafter.

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30 N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

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Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

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Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

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Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

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In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

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The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

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- | | |
|---|--------------------------------|
| EDC - 1-(3-dimethylaminopropyl)3-ethylcarbodiimide; | |
| DMF - dimethylformamide; | DMSO - dimethylsulphoxide; |
| HOBT - 1-hydroxybenzotriazole; | THF - tetrahydrofuran; |
| TFA - trifluoroacetic acid; | NMM - N-methylmorpholine; |
| 30 DCM - dichloromethane; | Ph - phenyl; |
| BOC - tert -butoxycarbonyl; | EtOAc - ethyl acetate; |
| MeOH - methanol; | LDA - lithium diisopropylamide |
| tyr - tyrosine; | Ar - aryl; |
| HetAr - heteroaryl; | pyr - pyridine; |
| 35 thiopro - thioproline; | Bu - butyl; |
| Me - methyl; | app - apparent |

INTERMEDIATE 1**2-Chloronicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester**

- 5 A solution of O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride, (1.11g, 2.84mmol), 2-chloronicotinic acid (0.45g, 2.84mmol), EDC (0.60g, 3.13mmol), HOBT (0.46g, 3.41mmol) and NMM (0.467ml, 0.43g, 4.26mmol) in DCM (25ml) was stirred at room temperature for 24 h. The reaction mixture was partitioned between DCM (50ml) and 10% NaHCO₃ solution (30ml). The organic layer was separated, dried over MgSO₄ and the solvent removed under vacuum to give a pale yellow solid that was recrystallised from EtOAc/hexane to give the title compound as an off white solid (1.14g, 81%). δ H (CDCl₃) 8.46 (1H, dd, \downarrow 2.0, 4.7Hz), 8.05 (1H, dd, \downarrow 2.0, 7.6Hz), 7.34 (2H, m), 7.25 (2H, m), 7.11 (2H, m), 6.96 (3H, m), 5.24 (2H, s), 5.06 (1H, m), 3.80 (3H, s) and 3.24 (2H, m).

INTERMEDIATE 2**2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester**

- 20 A solution of O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride (0.78g, 2.0mmol), EDC (0.42g, 2.2mmol) HOBT (0.32g, 2.4mmol) and NMM (0.55ml, 0.50g, 5.0mmol) in DMF (10ml) was treated with a solution of 2-thio(2,5-dimethoxyphenyl)nicotinic acid (0.58g, 2.0mmol) in DMF (2ml) and stirred for 16h at room temperature. Solvent was removed *in vacuo* and the residue was partitioned between EtOAc (50ml) and 10% hydrochloric acid (25ml). The organic layer was separated, washed with 10% NaHCO₃ solution (30ml), dried over MgSO₄ and the solvent removed *in vacuo* to give a yellow oil which was purified by chromatography (SiO₂; EtOAc/hexane 1:1) to give the title compound as a white foam (1.14g, 86%). δ H (CDCl₃) 8.39 (1H, dd, \downarrow 1.9, 4.7Hz), 7.85 (1H, dd, \downarrow 1.9, 7.7Hz), 7.47 (1H, d, \downarrow 7.6Hz), 7.37-6.81 (11H, m), 5.18 (2H, s), 5.09 (1H, m), 3.78 (6H, s), 3.53 (3H, s) and 3.25 (2H, m).

INTERMEDIATE 3

- 35 **2-Mercaptonicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester**

A solution of O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride (2.50g, 6.4mmol), 2-mercaptonicotinic acid (0.99g, 6.4mmol) and NMM (1.41ml, 1.29g, 12.8mmol) in DMF (10ml) was stirred at room temperature for 64h. Solvent was removed *in vacuo* and the residue partitioned between DCM (30ml) and water (25ml). The aqueous layer was extracted with DCM (30ml) and the combined organic layers were washed with 10% NaHCO₃ solution (30ml), dried over MgSO₄ and the solvent removed *in vacuo* to give a brown oil which was purified by chromatography (SiO₂; gradient elution, 4:1 EtOAc/hexane to 100% EtOAc) to give the title compound as a yellow foam, (2.92g, 93%). δ H (CDCl₃) 8.71 (1H, dd, \downarrow 1.8, 7.6Hz), 8.05 (1H, s), 7.61 (1H, dd, \downarrow 1.8, 6.1Hz), 7.35 (2H, m), 7.33-7.19 (2H, m), 6.94 (2H, d, \downarrow 8.7Hz), 5.22 (2H, s), 4.97 (1H, m), 3.74 (3H, s) and 3.21 (2H, m).

15 INTERMEDIATE 4

2-Thio(S-4-picolinyl)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester

A solution of Intermediate 3 (0.50g, 1.0mmol) and 4-picolyl chloride hydrochloride (0.17g, 1.0mmol) in DCM (10ml) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.31ml, 0.31g, 2.0mmol) and stirred at room temperature for 5h. The reaction was partitioned between water and DCM, the organic layer separated, dried over MgSO₄ and the solvent removed *in vacuo* to give a yellow gum that was purified by chromatography (SiO₂, EtOAc), to give a pale yellow solid, which was recrystallised from EtOAc/hexane (1:1) to give the title compound as an off white solid (0.30g, 52%). δ H (CDCl₃) 8.47(2H, m), 7.69 (1H, dd, \downarrow 1.8, 7.7Hz), 7.38-7.22 (6H, m), 7.06 (3H, m), 6.90 (2H, m), 6.62 (1H, d, \downarrow 7.5Hz), 5.23 (2H, s), 5.03 (1H, m), 4.40 (2H, m), 3.79 (3H, s), 3.28 (1H, dd, \downarrow 5.8, 14.1Hz) and 3.19 (1H, dd, \downarrow 5.4, 14.1Hz).

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INTERMEDIATE 5

2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-L-4-aminophenylalanine methyl ester

A solution of 4-amino-L-phenylalanine methyl ester dihydrochloride (0.53g, 2.0mmol), EDC (0.42g, 2.2mmol) HOBT (0.32g, 2.4mmol) and NMM (0.66ml, 0.61g, 6.0mmol) in DMF (10ml) was treated with a solution of 2-

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thio(2,5-dimethoxyphenyl)nicotinic acid (0.58g, 2.0mmol) in DMF (2ml) and stirred for 64h at room temperature. The solvent was removed *in vacuo*, and the residue partitioned between DCM (30ml) and water (20ml). The organic layer was separated, washed with 10% NaHCO₃ (20ml) solution, dried over MgSO₄ and the solvent evaporated *in vacuo* to give a brown gum which was purified by chromatography (SiO₂; EtOAc) to give the title compound as a yellow foam (0.67g, 72%). δ H (CDCl₃) 8.35 (1H, dd, \downarrow 1.8, 4.8Hz), 7.81 (1H, dd, \downarrow 1.9, 7.7Hz), 7.41 (1H, d, \downarrow 7.6Hz), 7.12 (1H, d, \downarrow 3.0Hz), 7.07-6.81 (5H, m), 6.49 (2H, d, \downarrow 8.4Hz), 5.00 (1H, m), 3.76 (3H, s), 3.74 (3H, s), 3.55 (3H, s) and 3.14 (2H, m).

INTERMEDIATE 6

2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester

A solution of Intermediate 5 (0.68g, 1.5mmol) and NMM (0.53ml, 0.49g, 4.8mmol) in DCM (20ml) was treated with 2,6-dichlorobenzoyl chloride (0.23ml, 0.33g, 1.6mmol) and the reaction stirred for 16h at room temperature, then partitioned between DCM (50ml) and 10% NaHCO₃ solution (30ml). The organic layer was separated, dried over MgSO₄ and the solvent evaporated *in vacuo* to give an off-white solid that was triturated with EtOAc/diethyl ether (2:1) to give the title compound as an off-white solid (0.44g, 46%). δ H (MeOH-*d*⁴) 8.28 (1H, dd, \downarrow 1.8, 4.9Hz), 7.70 (1H, dd, \downarrow 1.8, 7.6Hz), 7.58 (2H, d, \downarrow 8.6Hz), 7.48-7.38 (3H, m), 7.30 (2H, d, \downarrow 8.6Hz), 7.27 (1H, dd, \downarrow 4.9, 7.7Hz), 7.01 (1H, dd, \downarrow 1.1, 2.3Hz), 6.93 (2H, m), 4.87 (1H, m), 3.77 (3H, s), 3.75 (3H, s), 3.60 (3H, s), 3.32 (1H, m) and 3.13 (1H, dd, \downarrow 8.6, 14.0Hz).

INTERMEDIATE 7

O-(2,6-dichlorobenzyl)-N-(4-acetyl-1,2,5-trimethyl-3-pyrrolyl)-L-tyrosine methyl ester

NMM (155mg, 169 μ l, 1.54mmol), HOBT (227mg, 1.68mmol), 4-acetyl-1,2,5-trimethylpyrrole-3-carboxylic acid (300mg, 1.54mmol) and EDC (295mg, 1.54mmol) were added sequentially to a stirred solution of O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride (546mg, 1.40mmol) in dry DMF (15ml). The reaction was stirred at room temperature under N₂ for 18h. The solvent was removed *in vacuo* and the residue partitioned

between EtOAc (50ml), and 10% aqueous Na₂CO₃ (40ml). The phases were separated and the aqueous phase extracted with EtOAc (2 x 25ml). The combined organic extracts were washed consecutively with 5% aqueous hydrochloric acid (20ml), 10% aqueous Na₂CO₃ (20ml) and brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo*. The obtained orange foam (0.6g) was chromatographed (silica; 50% EtOAc/Hexane → 100% EtOAc) affording the title compound as a white foam (380mg, 51%); ¹Hnmr (d⁶DMSO) 8.53 (1H, d, \downarrow 8Hz, NH), 7.57-7.43 (3H, m's, aryl-H), 7.22 (2H, d, \downarrow 8.5Hz), aryl-H), 6.95 (2H, d, \downarrow 8.5Hz, aryl-H), 5.18 (2H, br s, CH₂-O), 4.67 (1H, m, α -tyr-H), 3.66 (3H, s, Me-O), 3.34 (3H, s, Me-N), 3.12 (1H, dd, \downarrow 4.1, 13.8Hz, CH_AH_BAr), 2.90 (1H, dd, \downarrow 11.3, 13.8Hz, CH_AH_BAr), 2.32 (3H, s, MeCO), 2.0 (3H, s, pyrrole-Me) and 1.94 (3H, s, pyrrole-Me). m/z (ES + 60V) 531 (MH⁺, 100), 533 (MH⁺, 75) 553 (MNa⁺, 15%).

15 INTERMEDIATE 8

2-Chloronicotiny-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester

EDC (270mg, 1.5mmol) was added to a stirred solution of (N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester (500mg, 1.3mmol), 2 chloronicotinic acid (200mg, 1.3mmol), HOBt (190mg, 1.5mmol) and NMM (423 μ l, 3.9mmol) in anhydrous DMF (2ml) at 0°. The DMF solution was stirred overnight at room temperature then the DMF was evaporated *in vacuo*. The residue was taken up in DCM (50ml), washed with water (3 x 10ml), saturated aqueous NaHCO₃ (2 x 10ml) and water (2 x 10ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂; 1:1 EtOAc: hexane) to give the title compound as a white foam (450mg, 80%). ¹H (CDCl₃), 8.50 (1H, m, pyr H), 8.05 (1H, d, \downarrow 9.2Hz, pyrH), 7.58 (2H, d, \downarrow 8.5Hz, ArH), 7.46 (1H, br s, NH), 7.36-7.24 (3H, m, 2ArH, 1pyrH), 7.21 (2H, d, \downarrow 8.5Hz, 2 ArH), 7.12 (1H, d, \downarrow 6.6Hz, NH), 5.05-5.18 (1H, m, CH α tyr), 3.81 (3H, s, CO₂Me) and 3.39-3.18 (2H, m, CH₂Ar).

INTERMEDIATE 9

Methyl-2-thio(S-acetate)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester

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A solution of Intermediate 3 (370mg, 0.76mmol) in anhydrous DMF (2ml) was added to a suspension of sodium hydride (60% in oil, 33mg, 0.83mmol) in anhydrous DMF (3ml) at 0°. The mixture was stirred for 10min at room temperature, then recooled to 0°. Methyl bromoacetate (115mg, 0.76mmol) was added dropwise, then the mixture was stirred overnight at room temperature. The mixture was quenched with water (0.5ml) and the DMF evaporated *in vacuo*. The residue was dissolved in EtOAc, washed with water (3 x 10ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂; EtOAc/hexane 1:1) to give the title compound as a white solid (360mg, 85%). δ H (CDCl₃) 8.45 (1H, m, pyrH), 7.71 (1H, d, \downarrow 7.7, pyrH), 7.35 (2H, d, \downarrow 7.3Hz, 2ArH), 7.28-6.9 (6H, m, 5ArH, 1pyrH), 6.71 (1H, d, \downarrow 7.5Hz, NH), 5.24 (2H, s, OCH₂Ar), 5.08-5.03 (1H, m, CH α tyr), 3.96 (2H, s, SCH₂), 3.78 (3H, s, CO₂CH₃), 3.71 (3H, s, CO₂CH₃), 3.31 (1H, dd, \downarrow 14, 5.4Hz, CH_AH_BAr) and 3.21 (1H, dd, \downarrow 14, 5.2Hz, CH_AH_BAr).

INTERMEDIATE 10

2-Thio(S-methyl)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester

EDC (540mg, 3mmol) was added to a stirred solution of (O-2,6-dichlorobenzyl)-L-tyrosine methyl ester (1g, 2.6mmol), 2 methylmercaptotnicotinic acid (433mg, 2.6mmol), HOBT (364mg, 2.6mmol) and NMM (846 μ l, 7.8mmol) in anhydrous DMF (4ml) at 0°. The DMF solution was stirred overnight at room temperature, then the DMF was evaporated *in vacuo*. The residue was taken up in DCM (70ml), washed with water (3 x 15ml), saturated aqueous NaHCO₃ (2 x 15ml) and water (2 x 15ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂; EtOAc) to give the title compound as a white solid (1.2gm, 92%). δ H (CDCl₃) 8.42 (1H, dd, \downarrow 1.7, 4.8, 1pyrH), 7.67 (1H, dd, \downarrow 1.7, 7.6, 1pyrH), 7.31 (2H, d, \downarrow 8.5, ArH), 7.18 (1H, dd, \downarrow 2.3, 8.5, ArH), 7.09 (3H, d, plus broad peak, \downarrow 8.6, 2ArH, 1NH), 6.97 (1H, m, 1pyrH), 6.88 (2H, d, \downarrow 8.6, 2ArH), 5.18 (2H, s, OCH₂Ar), 4.96 (1H, m, CH α tyr), 3.72 (3H, s, OCH₃), 3.25-3.04 (2H, m, CH₂Ar) and 2.47 (3H, s, SCH₃). m/z (ESI, GOU) 505 (MH⁺).

INTERMEDIATE 11

**Ethyl 3-(4-(((4-methoxybenzyl)oxy)carbonyl)phenyl)-2-
((diphenylmethylene)amino)propanoate**

N-(Diphenylmethylene) glycine ethyl ester (6.6g, 24.6mmol) and potassium carbonate (6.8g, 49mmol) were added to a solution of 4-methoxybenzyl-4-
5 (bromomethyl)benzoate (8.2g, 24.6mmol) in acetonitrile (200ml). The mixture was heated at reflux overnight, then filtered and the solvent removed *in vacuo* to give the title compound as a yellow oil (13.55g). δ H (CDCl₃, 300 MHz) 7.8 (2H, d, \downarrow 9.0Hz), 7.5 (10H, m), 7.3 (2H, d, \downarrow 9.0Hz), 6.9 (2H, d), 6.6 (2H, m), 5.23 (2H, s), 4.1 (3H, m), 3.7 (3H, s), 3.2 (2H, m)
10 and 1.2 (3H, m); m/z (ESI) 522 (MH⁺).

INTERMEDIATE 12

**Ethyl 2-amino-3-(4-(((4-methoxybenzyl)oxy)carbonyl)phenyl)
propanoate**

15 Hydrochloric acid (2M, 15.83ml, 1.5eq) was added to a solution of Intermediate 11 (11.0g, 21.12mmol) in THF (30ml). After 20min the reaction mixture was basified to pH7 with NaHCO₃ and the solvent removed *in vacuo*. The residue was taken up in EtOAc (300ml) and washed with water (200ml) and brine (200ml), dried (MgSO₄) and
20 evaporated *in vacuo*. Chromatography (SiO₂; EtOAc) gave the title compound as a yellow oil (4.91g, 65%). δ H (CDCl₃, 300MHz) 7.88 (2H, d, \downarrow 8.0Hz), 7.4 (4H, dd), 7.0 (2H, d, \downarrow 8.0Hz), 5.25 (2H, s), 4.05 (2H, q), 3.7 (3H, s), 3.57 (1H, t), 2.87 (2H, m) and 1.1 (3H, t), m/z (ESI) 358 (MH⁺).

25 **INTERMEDIATE 13**

**Ethyl-2-(((2-chloro-3-pyridinyl)carbonyl)amino)-3-(4-(((4-
methoxybenzyl)oxy)carbonyl)phenyl)propanoate**

EDC;HCl (591mg, 3.08mmol) and HOBT (416mg, 3.08mmol) were added to a solution of Intermediate 12 (1.0g, 2.8mmol), 2-chloronicotinic acid
30 (450mg, 2.86mmol) and NMM (370 μ l, 3.36mmol) in DMF (30ml). The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (300ml) and NaHCO₃ solution (300ml). The organic phase was washed with citric acid (10%, 2 x 200ml), NHCO₃ solution (200ml) and brine (300ml), dried
35 (MgSO₄) and concentrated *in vacuo* to give the title compound as a yellow oil (1.36g, 98%). δ H (CDCl₃, 300MHz) 9.12 (1H, d, \downarrow 8.0Hz), 8.47 (1H, m),

7.91 (2H, d, \downarrow 8.0Hz), 7.6 (1H, dd), 7.45 (5H, m), 6.95 (2H, d, \downarrow 8.0Hz), 4.67 (1H, m), 4.15 (2H, m), 3.75 (3H, s), 3.31 (1H, m), 3.23 (1H, m) and 1.17 (3H, s); m/z (ESI) 497 (MH⁺).

5 **INTERMEDIATE 14**

Ethyl 2-[(2-chloro-3-pyridinyl)carbonylamino]-3-[4-(carboxyl)phenyl]propanoate

TFA (20ml) was added to a solution of Intermediate 13 (1.36g, 2.75mmol) in toluene (20ml). The reaction mixture was stirred for 30min at room temperature. The white solid obtained was recrystallised (EtOAc/hexane) to give the title compound (1.04g, 100%). δ H (CDCl₃, 300MHz) 12.84 (1H, br s), 9.1 (1H, d, \downarrow 8.0Hz), 8.47 (1H, m), 7.87 (2H, d, \downarrow 8.0Hz), 4.1 (2H, m), 3.2 (1H, m), 3.07 (1H, m) and 1.17 (3H, m); m/z (ESI) 377 (MH⁺).

15 **INTERMEDIATE 15**

Ethyl 2-[(2-chloro-3-pyridinyl)carbonylamino]-3-[4-[(2,6-dichloroanilino)carbonyl]phenyl]propanoate

Carbon tetrachloride (5ml) was added to a suspension of Intermediate 14 (1.04g, 2.76mmol) and triphenylphosphine (0.87g, 3.31mmol) in acetonitrile. The reaction mixture was stirred for 2h at room temperature. 2,6-Dichloroaniline (0.89g, 5.52mmol) and NMM (455 μ l, 4.14mmol) were added and the mixture stirred for a further 48h at room temperature. The solvent was removed *in vacuo* and the residue partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (x 2) and the combined organic extracts washed with water (x 2) and saturated aqueous NaHCO₃ (x2), dried (Na₂SO₄) and concentrated *in vacuo*. Chromatography (SiO₂; EtOAc/hexane 50:50) gave the title compound (924mg) δ H (CDCl₃, 300MHz) 8.46 (1H, s), 8.05 (1H, d, \downarrow 7.4Hz), 7.89 (2H, d, \downarrow 7.9Hz), 7.69-7.10 (8H, m), 5.11 (1H, dt, \downarrow 6.7, 5.8Hz), 4.25 (2H, q, \downarrow 7.1Hz), 3.42 (1H, dd, \downarrow 13.9, 5.8Hz), 3.31 (1H, dd, \downarrow 13.9, 5.8Hz) and 1.30 (3H, t, \downarrow 7.1Hz).

INTERMEDIATE 16

Methyl 4-[2(2,6-dichlorophenyl)-2-hydroxyethyl]benzoate

35 A solution of methyl 4-(bromomethyl)benzoate (2.0g, 8.7mmol) in THF (4.4ml) was added slowly to cut zinc foil (683mg, 10.44mmol) which had

been activated with 1,2-dibromoethane (80mg). After 3h of stirring at room temperature 2ml of the solution was transferred to a solution of copper cyanide (396mg, 4.4mmol) and lithium chloride (356mg, 8.4mmol) in THF (4ml) cooled to -78°. This solution was warmed to -20° and then cooled back to -78°. Boron trifluoride etherate (983µl, 8mmol) was then added followed by 2,6-dichlorobenzaldehyde (0.56g, 3.2mmol) in THF (1ml). The reaction was stirred for 2h and then allowed to warm slowly to room temperature. Water (20ml) was then added and the reaction mixture extracted into EtOAc (3 x 25ml) and the combined organics dried (Na₂SO₄) and evaporated. Purification by column chromatography (SiO₂; hexane:EtOAc, 4:1) gave the title compound as a colourless oil (863mg, 83%). δH (CDCl₃) 7.95 (2H, m, ArH), 7.93-7.26 (4H, m, ArH), 7.17-7.12 (1H, m, ArH), 5.73-5.65 (1H, m, CH), 3.91 (3H, s, CO₂Me), 3.43 (1H, dd, J 13.5, 8.4Hz, CH_AH_B) and 3.28 (1H, dd, J 13.5, 6.3Hz, CH_AH_B), m/z (ESI, 60V) 325 (MH⁺).

INTERMEDIATE 17

Methyl 4-[2-[(tert-butyl(dimethyl)silyl]oxy]-2-(2,6-dichlorophenyl)ethyl]benzoate

To a solution of Intermediate 16 (20g, 6.15mmol) in DCM (10ml) cooled to 0° was added 2,4,6-collidine (2.03ml, 15.39mmol). After 15min *tert*-butyldimethylsilyltrifluoromethanesulphonate (2.12ml, 9.23mmol) was added. The reaction mixture was stirred overnight at room temperature then diluted with DCM (100ml) and washed with 1M hydrochloric acid (50ml), water (50ml) and brine (50ml), dried (Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (SiO₂; hexane:EtOAc, 5:1) gave the title compound as a pale pink oil (2.67g, 100%). δH (CDCl₃) 7.94 (2H, d, J 6.5Hz, ArH), 7.33, 7.21 (4H, m, ArH), 7.13-7.07 (1H, m, ArH), 5.58 (1H, dd, J 9.4, 4.6Hz, CH), 3.90 (1H, s, CO₂Me), 3.46 (1H, dd, J 13.1, 9.4Hz, CH_AH_B), 3.04 (1H, dd, J 13.1, 4.6Hz, CH_AH_B), 0.74 (9H, s, Si^tBu), -0.31 (3H, s, SiMe) and -0.32 (3H, s, SiMe); m/z (ESI, 60V) 361 (MH⁺).

INTERMEDIATE 18

4-[2-[(Tert-butyl(dimethyl)silyl]oxy]-2-(2,6-dichlorophenyl)ethyl]benzoic acid

Lithium aluminium hydride (1M solution in THF, 6.46ml, 6.46mmol) was added to an ice cold solution of Intermediate 17 (2.67g, 6.15mmol) in THF (20ml). The reaction mixture was stirred for 1h then quenched with the addition of water and extracted into DCM (3 x 50ml), dried (Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (SiO₂; hexane:EtOAc, 4:1) gave the title compound as a colourless oil (2.9g, 87%) δ H 7.32-7.06 (7H, m, ArH), 5.56 (1H, dd, J 9.3, 4.7Hz, CH₂CH), 4.65 (2H, d, J 5.9Hz, CH₂O), 3.39 (1H, dd, J 13.2, 9.3Hz, CH_AH_B), 3.01 (1H, dd, J 13.2, 4.7Hz, CH_AH_B), 0.75 (9H, s, Si^tBu), -0.29 (3H, s, SiMe) and -0.31 (3H, s, SiMe); m/z (ESI, 60V) 433 (MH⁺).

INTERMEDIATE 19

4-[2-([Tert-butyl(dimethyl)silyl]oxy)-2-(2,6-dichlorophenyl)ethyl]benzylbromide

A solution of triphenylphosphine (843mg, 3.21mmol) in DCM (2ml) was added to a solution of carbon tetrabromide (1.42g, 3.73mmol) and Intermediate 18 (1.10g, 2.67mmol) in DCM (3ml) and stirred at room temperature for 24h. Ether (100ml) was added and the solid precipitate formed removed by filtration. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂; 8:1, hexane:EtOAc) to give the title compound (1.20g, 95%). δ H (CDCl₃) 7.32-7.07 (7H, m, ArH), 5.54 (1H, dd, J 9.5, 4.4Hz, CH₂CH), 4.49 (2H, s, CH₂Br), 3.39 (1H, dd, J 13.2, 9.5Hz, CH_AH_B), 2.96 (1H, dd, J 13.2, 4.4Hz, CH_AH_B), 0.73 (9H, s, Si^tBu), -0.31 (3H, s, SiMe) and -0.32 (3H, s, SiMe); m/z (ESI, 60V) 474 (MH⁺).

INTERMEDIATE 20

4-[2-([Tert-butyl(dimethyl)silyl]oxy)-2-(2,6-dichlorophenyl)ethyl]phenylalanine ethyl ester

To a solution of ethyl *N*-(diphenylmethylene)glycinate (2.63g, 9.81mmol) in THF (50ml) cooled to -78° was added lithium diisopropylamine (2M in heptane/THF/ethylbenzene, 5.64ml, 11.28mmol). The solution was stirred for 45min. Intermediate 19 (4.20g, 8.92mmol) in THF (20ml) was then added dropwise. The reaction mixture was stirred for 2h at -78° and then warmed to room temperature. EtOAc (100ml) was added and the mixture washed with water (75ml) and brine (75ml), dried (Na₂SO₄) and

evaporated under reduced pressure. The residue was then taken up in acidic ethanol and stirred for 10min. The volatiles were then removed and the residue partitioned between EtOAc (150ml) and saturated aqueous Na₂CO₃ (100ml). The aqueous layer was extracted several times with EtOAc and the combined organics dried (Na₂SO₄) and evaporated under reduced pressure. The remaining residue was purified by column chromatography (SiO₂; EtOAc) to give the title compound as a colourless oil (3.95g, 95%). δ H (CDCl₃) 7.32-7.05 (7H, m, ArH), 5.52 (1H, dd, \downarrow 9.4, 4.6Hz, CHOSi), 4.18 (2H, q, \downarrow 7.1Hz, CO₂CH₂CH₃), 3.68 (1H, dd, \downarrow 7.9, 5.1Hz, CHNH₂), 3.35 (1H, dd, \downarrow 13.2, 9.4Hz, CHOSiCH_AH_B), 3.07 (1H, dd, \downarrow 13.5, 5.1Hz, CHNH₂CH_AH_B), 2.95 (1H, dd, \downarrow 13.2, 4.6Hz, CHOSiCH_AH_B), 2.95 (1H, dd, \downarrow 13.2, 4.6Hz, CHOSiCH_AH_B), 2.82 (1H, dd, \downarrow 13.5, 7.9Hz, CHNH₂CH_AH_B), 1.53 (2H, br s, NH₂), 1.27 (3H, t, \downarrow 7.1Hz, CO₂CH₂CH₃), 0.74 (9H, s, Si^tBu) and -0.32 (6H, s, SiMe₂); m/z (ESI, 60V) 496 (MH⁺).

INTERMEDIATE 21

{4-[2-([Tert-butyl(dimethyl)silyl]oxy)-2-(2,6-dichlorophenyl)ethyl]}-(N-2-chloronicotinoyl)phenylalanine ethyl ester

To a solution of Intermediate 20 (1.50g, 3.20mmol) and 2-chloronicotinic acid (504mg, 3.20mmol) in DCM (75ml) at room temperature was added NMM (386 μ l, 3.53mmol), EDC (675mg, 3.53mmol) and HOBt (477mg, 3.53mmol). The reaction mixture was stirred overnight at room temperature and then diluted with DCM (50ml) and washed with saturated aqueous Na₂CO₃ (50ml), water (50ml) and brine (50ml), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂; EtOAc) to give the title compound as a white solid (1.72g, 85%). δ H (CDCl₃) 8.41-8.38 (1H, m, NH), 8.01-7.96 (1H, m, ArH), 7.29-6.97 (9H, m, ArH), 5.47 (1H, dd, \downarrow 9.2, 4.7Hz, CHOSi), 5.24-4.96 (1H, m, CHNH), 4.19 (2H, qd, \downarrow 7.1, 1.1Hz, CO₂CH₂CH₃), 3.34-3.14 (4H, m, CH₂ x 2), 1.27 (3H, td, \downarrow 7.1, 1.3Hz, CO₂CH₂CH₃), 0.69 (s) and 0.66 (s); together (9H, Si^tBu) and -0.38 (s) and -0.40 (s); together (6H, SiMe₂); 659 (M⁺⁺ Na⁺).

INTERMEDIATE 22

(N-2-Chloronicotinoyl)-4-[2-(2,6-dichlorophenyl)-2-hydroxyethyl]phenylalanine ethyl ester

5 Tributylammonium fluoride (1M in THF, 4.7ml, 4.70mmol) was added to a solution of Intermediate 21 (1.50g, 2.35mmol) in THF (75ml) at room temperature. The reaction mixture was stirred for 2h and then the THF removed and the residue partitioned between EtOAc and water. The layers were separated and the aqueous layer extracted with EtOAc. The combined organics were dried (Na₂SO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO₂; 10 MeOH:DCM, 5:95) gave the title compound as a pale brown oil (1.03g, 84%) δ H (CDCl₃) 8.31-8.29 (1H, m, NH), 7.86-7.82 (1H, m, ArH), 7.25-6.96 (9H, m, ArH), 5.54-5.49 (1H, m, CH), 4.94-4.88 (1H, m, CH), 4.11 (2H, qd, \downarrow 7.1, 2.0Hz, CO₂CH₂CH₃), 3.28-3.03 (4H, m, 2 x CH₂) and 1.19 (3H, td, \downarrow 7.1, 1.1Hz, CO₂CH₂CH₃); m/z (ESI, 60V) 521 (MH⁺).

INTERMEDIATE 23

(N-2-Chloronicotinoyl)-4-[2-(2,6-dichlorophenyl)-2-oxoethyl]phenylalanine ethyl ester

20 To a solution of Intermediate 22 (300mg, 0.58mmol) in acetone (20ml) was added Jones' Reagent dropwise until an orange colour persisted. i-Propyl alcohol was added to use up excess reagent and then the solution was basified by the addition of saturated aqueous Na₂CO₃ solution. The solution was then decanted from the solids and the acetone removed *in vacuo*. The remaining aqueous solution was then extracted with ether (x 25 2) and the combined organics dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂; hexane:EtOAc, 3:2) to give the title compound as a colourless oil (200mg, 67%). δ H (CDCl₃) 8.40 (1H, dd, \downarrow 4.8, 2.0Hz), 7.94 (1H, dd, \downarrow 7.7, 2.0Hz), 7.38-7.11 (8H, m, ArH), 7.02 (1H, d, \downarrow 7.5Hz, ArH), 4.19 (2H, q, \downarrow 7.2Hz, CO₂CH₂CH₃), 4.09 (2H, s, CH₂CO), 3.28 (1H, dd, \downarrow 14.0, 5.9Hz, CH_AH_B), 3.18 (1H, dd, \downarrow 14.0, 6.1Hz, CH_AH_B) and 1.26 (5H, t, \downarrow 7.2Hz, CO₂CH₂CH₃); m/z (ESI, 60V) 519 (MH⁺).

INTERMEDIATE 24

35 **Methyl 4-[(E)-2-(2,6-dichlorophenyl)ethenyl]benzoate**

A solution of Intermediate 16 (2.0g, 6.15mmol) in toluene (25ml) containing p-toluen sulphonic acid (100mg) was heated to reflux in a Dean-Stark apparatus for 4h. Toluene was then removed under reduced pressure and the residue purified by column chromatography (SiO₂; hexane:EtOAc, 5:1) to give the title compound as an off white solid (1.64g, 87%); δ H (CDCl₃) 8.05 (2H, d, \downarrow 8.3Hz), 7.60 (2H, d, \downarrow 8.3Hz, ArH), 7.36 (2H, d, \downarrow 8.0Hz), 7.21 (2H, d, \downarrow 1.7Hz), 7.15-7.10 (1H, m), and 3.93 (3H, s, CO₂CH₃); m/z (ESI, 60V) 329 (MH⁺).

10 INTERMEDIATE 25

4-[(E)-2-(2,6-Dichlorophenyl)ethenyl]benzyl alcohol

To an ice cold solution of Intermediate 24 (1.56g, 5.08mmol) in THF (20ml) was added lithium aluminium hydride (1M in THF, 5.34ml, 5.34mmol). The reaction mixture was stirred for 30min and then quenched by the addition of water (10ml). The resulting biphasic solution was filtered through Celite® and then extracted with DCM (2 x 50ml). The combined organics were dried (Na₂SO₄) and evaporated under reduced pressure to give the title compound as a colourless oil which solidified on standing (1.5g, 99%). δ H (CDCl₃) 7.55 (2H, d, \downarrow 8.2Hz), 7.42-7.33 (4H, m), 7.20-7.08 (3H, m) and 4.75 (2H, d, \downarrow 5.3Hz, CH₂); m/z (ESI, 60V) 301 (M⁺ + Na⁺).

INTERMEDIATE 26

4-[(E)-2-(2,6-Dichlorophenyl)ethenyl]benzyl bromide

A solution of triphenylphosphine (1.58g, 6.04mmol) in DCM (10ml) was added to a solution of Intermediate 25 (1.40g, 5.03mmol) and carbon tetrabromide (2.33g, 7.04mmol) in DCM (10ml). The resulting solution was stirred for 1h and then diluted with ether (150ml) and the resulting solid removed by filtration. The filtrate was then evaporated under reduced pressure and the resulting residue purified by column chromatography (SiO₂; hexane: EtOAc, 6:1) to give the title compound as a colourless oil (1g, 49%). δ H (CDCl₃) 7.55 (2H, d, \downarrow 8.3Hz), 7.44-7.32 (3H, m), 7.23-7.09 (4H, m) and 4.53 (2H, s, CH₂); m/z (ESI, 60V) 342 (MH⁺)

INTERMEDIATE 27

35 4-[(E)-2-(2,6-Dichlorophenyl)ethenyl]phenylalanine ethyl ester

To a solution of ethyl *N*-(diphenylmethylene)glycinate (860mg, 3.21mmol) in THF (20ml) cooled to -78° was added lithium diisopropylamine (2M in heptane/THF/ethylbenzene, 1.68ml, 3.36mmol). The solution was stirred for 45min. Intermediate 26 (10g, 2.92mmol) in THF (2ml) was added and the resulting reaction mixture stirred for 2h at -78° and then warmed to room temperature. EtOAc (100ml) was added and the mixture washed with water (75ml) and brine (75ml), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was then taken up in acidic ethanol and stirred for 1min. The volatiles were then removed and the residue partitioned between EtOAc (150ml) and saturated aqueous Na₂CO₃ (100ml). The aqueous layer was extracted several times with EtOAc and the combined organics dried (Na₂SO₄) and evaporated under reduced pressure. The remaining residue was purified by column chromatography (SiO₂; EtOAc) to give the title compound as a colourless oil (860mg, 81%). δ H (CDCl₃) 7.47 (2H, d, \downarrow 8.1Hz), 7.32 (2H, d, \downarrow 8.1Hz), 7.21 (2H, d, \downarrow 8.2Hz), 7.19-6.98 (3H, m), 4.18 (2H, q, \downarrow 7.1Hz, CO₂CH₂CH₃), 3.71 (1H, dd, \downarrow 7.8, 5.3Hz, CH), 3.10 (1H, dd, \downarrow 13.5, 5.3Hz, CH_AH_B), 2.88 (1H, dd, \downarrow 13.5, 7.8Hz, CH_AH_B) and 1.26 (3H, t, \downarrow 7.1Hz, CO₂CH₂CH₃); *m/z* (ESI, 60V) 364 (MH⁺)

20

INTERMEDIATE 28

(*N*-2-Chloronicotinoyl)-4-[(*E*)-2-(2,6-dichlorophenyl)ethenyl]phenylalanine ethyl ester

To a solution of Intermediate 27 (860mg, 2.36mmol) and 2-chloronicotinic acid (372mg, 2.36mmol) in DCM (25ml) was added NMM (285 μ l, 2.60mmol), EDC (498mg, 2.60mmol) and HOBt (352mg, 2.60mmol). The resulting solution was stirred for 3h and then diluted with DCM (50ml) and brine (50ml), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂; EtOAc) to give the title compound as a pale yellow oil (1.1g, 93%). δ H (CDCl₃), 8.43 (1H, dd, \downarrow 4.8, 2.0Hz), 8.02 (1H, dd, \downarrow 7.6, 2.0Hz), 7.46 (2H, d, \downarrow 8.2Hz), 7.34-6.92 (9H, m), 5.10-5.03 (1H, m, CH), 4.24 (2H, q, \downarrow 7.1Hz, CO₂CH₂CH₃), 3.33 (1H, dd, \downarrow 13.9, 5.8Hz, CH_AH_B), 3.24 (1H, dd, \downarrow 13.9, 5.8Hz, CH_AH_B) and 1.30 (3H, t, \downarrow 7.1Hz, CO₂CH₂CH₃); *m/z* (ESI, 60V) 503.5 (MH⁺).

35

INTERMEDIATE 29

N-(2-Chloronicotinoyl)-L-tyrosine methyl ester

EDC.HCl (2.11g, 11mmol) was added to a mixture of L-tyrosine methyl ester hydrochloride (2.32g, 10mmol), 2-chloronicotinic acid (1.58g, 10mmol), HOBT (1.49g, 11mmol) and NMM (2.31ml, 21mmol) in DMF (50ml). The mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*, the residue dissolved in EtOAc (300ml) and washed with dilute HCl (100ml), saturated aqueous NaHCO₃ (100ml), water (3 x 100ml) and brine (50ml), dried (Na₂SO₄) and solvent removed *in vacuo* to give the title compound as a yellow gum (3.27g, 98%). ¹H (DMSO-d₆, 300MHz) 9.21 (1H, s, OH), 9.03 (1H, d, \downarrow 7.9Hz, CONH), 8.45 (1H, dd, \downarrow 4.8, 1.9Hz, pyrH), 7.67 (1H, dd, \downarrow 7.4, 1.9Hz, pyrH), 7.47 (1H, dd, \downarrow 7.5, 4.8Hz, pyrH), 7.05 (2H, d, \downarrow 8.5Hz, ArH), 6.67 (2H, d, \downarrow 8.5Hz, ArH), 4.58 (1H, ddd, \downarrow 9.6, 7.9, 5.4Hz, CH α), 3.65 (3H, s, CO₂Me), 3.01 (1H, dd, \downarrow 13.9, 5.4Hz, CH_AH_BAr) and 2.85 (1H, dd, \downarrow 13.9, 9.6Hz, CH_AH_BAr); *m/z* (ESI, 60V) 335 (MH⁺).

INTERMEDIATE 30**N-(2-Chloronicotinoyl)-O-(2,6-dichlorobenzoyl)-L-tyrosine methyl ester**

A solution of Intermediate 29 (919mg, 2.75mmol) in DMF (10ml) was added to a suspension of sodium hydride (60% in mineral oil, 3.03mmol, 121mg) in DMF (20ml) at 0°. After 15min, 2,6-dichlorobenzoyl chloride (414 μ l, 2.89mmol) was added and the mixture stirred for 2h at room temperature. Water (~5ml) was added and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (150ml), washed with water (3 x 50ml) and brine (50ml), dried (Na₂SO₄) and evaporated *in vacuo*. Chromatography (SiO₂; DCM/MeOH, 98:2) gave the title compound as a white foam (1.10g, 79%). ¹H (DMSO-d₆, 300MHz) 9.12 (1H, d, \downarrow 7.6Hz, CONH), 8.45 (1H, dd, \downarrow 4.8, 2.0Hz, pyrH), 7.69-7.58 (4H, m, pyrH + Cl₂ArH₃), 7.46 (1H, dd, \downarrow 7.5, 4.9Hz, pyrH), 7.43 (2H, d, \downarrow 8.4Hz, ArH₂), 7.23 (2H, d, \downarrow 8.5Hz, ArH₂), 4.73 (1H, m, CH α), 3.68 (3H, s, CO₂Me), 3.22 (1H, dd, \downarrow 13.9, 5.2Hz, CH_AH_BAr) and 3.02 (1H, dd, \downarrow 13.9, 10.1Hz, CH_AH_BAr); *m/z* (ESI, 60V) 507 (MH⁺).

INTERMEDIATE 31

N-(2-Chloronicotinoyl)-N-methyl-N'-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine methyl ester

2-Chloronicotinoyl chloride (132mg, 0.75mmol) was added to N-methyl-N'-(3,5-dichloroisonicotinyl)-L-4-aminophenylalanine methyl ester [prepared from N-Boc-N'-phthaloyl-4-amino-L-phenylalanine methyl ester and methyl iodide, followed by treatment with hydrazine monohydrate and reaction with 3,5-dichloroisonicotinyl chloride with subsequent removal of the Boc group] and NMM (165μl, 1.5mmol) in DCM (10ml). The mixture was stirred for 1h at room temperature then diluted with DCM (100ml) and washed with dilute HCl (30ml), dried (Na₂SO₄) and evaporated *in vacuo*. Chromatography (SiO₂; EtOAc/hexane, 10:90) gave the title compound as a colourless gum (380mg, 97%). δH (DMSO-d₆, 300MHz, 405K) 10.35 (1H, br s, CONH), 8.67 (2H, s, Cl₂pyrH), 8.42 (1H, t, \downarrow 3.4Hz, ClpyrH), 7.55 (2H, br d, \downarrow 7.2Hz, ArH), 7.45-7.15 (4H, v br m, ArH + ClpyrH), 5.3 (1H, v br s, CH α), 3.74 (3H, s, CO₂Me), 3.4-3.3 (1H, br m, CH_AH_BAr), 3.16 (1H, dd, \downarrow 14.4, 9.6Hz, CH_AH_BAr) and 2.73 (3H, br s, NMe); m/z (ESI, 60V) 521 (MH⁺).

INTERMEDIATE 32

[(S-2,5-dimethoxyphenyl)sulphonyl]nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester

A solution of Intermediate 2 (0.79g, 1.26mmol) in DCM (50ml) was treated with 3-chloroperoxybenzoic acid (2.17g, 12.6mmol) and stored at 4° for 48h. The reaction was partitioned between DCM (20ml) and NaHCO₃ solution (20ml). The aqueous layer was extracted with DCM (25ml) and the combined organic layers washed with 10% aqueous Na₂SO₃ (50ml), dried (MgSO₄) and the solvent removed *in vacuo* to give a yellow foam that was purified by chromatography (SiO₂; EtOAc/hexane 3:1) to give the title compound as a white foam, (0.50g, 60%). δH (CDCl₃) 8.58 (1H, dd, \downarrow 4.7, 1.7Hz, pyr-H), 7.95 (1H, dd, \downarrow 7.8, 1.7Hz, pyr-H), 7.70 (1H, d, \downarrow 3.2Hz, Ar-H), 7.50 (1H, dd, \downarrow 7.8, 4.7Hz, pyr-H), 7.36-7.11 (6H, m, Ar-H), 7.01 (1H, d, \downarrow 7.6Hz, NH), 6.92-6.84 (3H, m, Ar-H), 5.21 (2H, s, CH₂O), 5.10 (1H, m, CH α), 3.85 (3H, s, OMe), 3.74 (3H, s, OMe), 3.49 (3H, s, CO₂Me) and 3.27 (2H, m, CHCH₂Ar). m/z (ESI, 60V) 659 (MH⁺).

EXAMPLE 1**2-Chloronicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine**

A solution of Intermediate 1 (0.20g, 0.41mmol) in THF (5ml) and water (5ml) was treated with lithium hydroxide monohydrate (25ml, 0.61mmol, 1.5 equiv.) and stirred at room temperature for 1.5h. The reaction was acidified to pH1 with 10% hydrochloric acid to give a white precipitate which was isolated by filtration, washed with water (5ml) and diethyl ether (5ml) and dried under vacuum to give the title compound as a white powder (0.14g, 72%). δ H (DMSO- d_6) 8.93 (1H, d, J 8.1Hz), 8.45 (1H, dd, J 2.0, 4.8Hz), 7.66 (1H, dd, J 2.0, 7.5Hz), 7.56 (2H, m), 7.47 (2H, m), 7.24 (2H, d, J 8.6Hz), 6.99 (2H, d, J 8.6Hz), 5.20 (2H, s), 4.60 (1H, d), 3.13 (1H, ABX, J 4.7, 13.9Hz) and 2.90 (1H, ABX, J 10.0, 13.9Hz). m/z (ES+, 60V) 479, 481 (MH⁺).

EXAMPLE 2**2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine hydrochloride**

A solution of Intermediate 2 (0.35g, 0.56mmol) in THF (15ml) and water (7.5ml) was treated with lithium hydroxide monohydrate (28mg, 0.67mmol) and stirred at room temperature for 16h. The reaction was acidified to pH1 with 10% hydrochloric acid, extracted with DCM (2 x 30ml), and the combined organic layers were dried over MgSO₄, the solvent removed *in vacuo* to give a gummy residue, which was purified by chromatography (SiO₂; 7.5% MeOH/DCM) to give a gum which was dissolved in acetonitrile (20ml) and water (20ml) and lyophilised to give the title compound as a white powder (0.26g, 71%). δ H (DMSO- d_6) 8.71 (1H, m), 8.29 (1H, dd, J 1.7, 4.8Hz), 7.75 (1H, d, J 6.0Hz), 7.56-6.94 (11H, m), 5.16 (2H, s), 4.56 (1H, m), 3.68 (3H, s), 3.60 (3H, s) and 3.21-1.96 (2H, m). m/z (ES+ 60V) 613, 615 (MH⁺).

EXAMPLE 3**a) 2-Thio(S-4-picolinyl)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine**

A solution of Intermediate 4 (0.30g, 0.52mmol) in THF (7.5ml) and water (5ml) was treated with lithium hydroxide monohydrate (33mg, 0.7mmol) and stirred at room temperature for 16h. The pH was adjusted to 6.5-7 with 10% hydrochloric acid to give a yellow precipitate which was isolated

by filtration, washed with water and dried *in vacuo* to give the title compound as a yellow powder (0.28g, 95%). δ H (DMSO- d_6) 8.83 (1H, d, \downarrow 8.0Hz), 8.50 (3H, m), 7.75 (1H, d, \downarrow 7.6Hz), 7.56-7.20 (8H, m), 6.95 (2H, d, \downarrow 8.5Hz), 5.17 (2H, s), 4.54 (1H, m), 4.37 (2H, s), 3.12 (1H, m) and 2.97 (1H, m). m/z (ES+, 60V) 568, 570 (MH+).

The following compounds were prepared in a similar manner by hydrolysis of the corresponding methyl ester. Each ester starting material was obtained either by alkylation of Intermediate 3 or alternative mercaptopyridine using the reagents shown using a similar procedure to that described for Intermediate 4:

b) 2-Thio-S-benzyl-nicotinoyl-(0-2,6-dichlorobenzyl)-L-tyrosine

ester from Intermediate 3 and benzyl chloride. δ H (DMSO- d_6) 8.78 (1H, d, \downarrow 8.1Hz, pyr-H), 8.54 (1H, dd, \downarrow 4.8, 1.1Hz, pyr-H), 7.69 (1H, dd, \downarrow 7.7, 1.7Hz, pyr-H), 7.68-7.17 (11H, m, Ar-H), 6.94 (2H, d, \downarrow 8.6, Ar-H), 5.16 (2H, s, CH₂O), 4.53 (1H, m, CH α), 4.34 (2H, s, CH₂Ar), 3.10 (1H, dd, \downarrow 13.9, 4.6Hz, CHCH_AH_BAr), 2.94 (1H, dd, \downarrow 13.9, 10.2Hz, CHCH_AH_BAr); m/z (ESI, 60V) 567 (MH+).

c) 2-Thio-(S-4-Methylphenyl)-nicotinoyl-(0-2,6-dichlorobenzyl)-L-tyrosine

ester from Intermediate 3 and 4-methylbenzyl chloride. δ H (DMSO- d_6) 8.87 (1H, d, \downarrow 8.1Hz, pyr-H), 8.31 (1H, dd, \downarrow 4.7, 1.8Hz, pyr-H), 7.70 (1H, dd, \downarrow 7.6, 1.7Hz, pyr-H), 7.54 (2H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.32-7.17 (7H, m, Ar-H), 6.98 (2H, d, \downarrow 8.6Hz, Ar-H), 5.17 (2H, s, CH₂O), 4.58 (1H, m, CH α), 3.16 (1H, dd, \downarrow 14.6, 14.0Hz, CHCH_AH_BAr), 2.98 (1H, dd, \downarrow 14.0, 10.1Hz, CHCH_AH_BAr) and 2.32 (3H, s, Me); m/z (ESI, 60V) 569 (MH+).

d) 2-Thio-S-(3-picolyl)-nicotinoyl-(0-2,6-dichlorobenzyl)-L-tyrosine

ester from Intermediate 3 and 3-picolyl chloride. δ H (DMSO- d_6) 9.04-8.54 (5H, m, Ar-H), 7.95-7.84 (2H, m, Ar-H), 7.56-7.43 (3H, m, Ar-H), 6.96 (2H, d, \downarrow 8.3Hz, Ar-H), 5.17 (2H, s, CH₂O), 4.55 (1H, m, CH α), 4.48 (2H, s, CH₂pyr), 3.05 (2H, m, CHCH₂Ar); m/z (ESI, 60V) 569 (MH+).

e) N-[2-thio(S-3-picolinyl)nicotinoyl]-0-2,6-dichlorobenzyl-L-tyrosine

ester from Intermediate 3 and 3-picolyl chlorid using DBU as base. δ H (DMSO- d_6) 8.8 (1H, br d), 8.57 (1H, m), 8.50 (1H, m), 7.72 (2H, m), 7.55 (2H, d), 7.5-7.4 (2H, m), 7.3-7.15 (4H, m), 6.95 (2H, d), 5.15 (2H, s), 4.55-4.45 (3H, m), 3.2-3.1 (1H, m), 3.0-2.9 (1H, m); m/z (ESI, 60V) 568 (MH⁺).

5

f) N-2-Thio(S-4-butanolate)nicotinoyl]-(O-2,6-dichlorobenzyl)-L-tyrosine

ester from Intermediate 3 and methyl-4-chlorobutyrate using K₂CO₃ as base. δ H (DMSO- d_6) 8.76 (1H, d, \downarrow 8.1Hz), 8.49 (1H, dd, \downarrow 4.8, 1.7Hz), 7.61 (1H, dd, \downarrow 7.7, 1.7Hz), 7.55 (2H, d, \downarrow 8.9Hz), 7.45 (1H, m), 7.23 (2H, d, \downarrow 8.5Hz), 7.2 (1H, m), 6.96 (2H, d, \downarrow 8.5Hz), 5.18 (2H, s), 4.53 (1H, m), 3.17-2.87 (4H, m), 2.40-2.30 (2H, t, \downarrow 7.3Hz), 1.83 (2H, m); m/z (ESI, 60V) 563 (MH⁺).

10

15 g) (N'-3,5-Dichloroisonicotinoyl)-N-([3-pyridinylmethyl]thio)isonicotinoyl]-L-4-aminophenylalanine

ester from 2-mercaptoisonicotinoyl-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine and 3-picolyl chloride. δ H (DMSO- d_6) 10.86 (1H, s, CO₂H), 8.92-8.75 (3H, m, ArH), 8.68-8.52 (2H, m), 8.39 (1H, br s), 7.75 (2H, t, \downarrow 7.5Hz), 7.56 (2H, d, \downarrow 6.3Hz), 7.39-7.18 (4H, m), 4.60-4.47 (1H, m, CH) and 3.25-2.92 (2H, m, CH₂); m/z (ESI, 60V) 582 (MH⁺).

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EXAMPLE 4

a) 2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine

25

A solution of Intermediate 6 (0.44g, 0.69mmol) in THF (7.5ml) and water (5ml) was treated with lithium hydroxide monohydrate (43mg, 1.0mmol) and stirred at room temperature for 16h, then acidified to pH1 with 10% hydrochloric acid. The mixture was extracted with DCM (2 x 30ml) and the solvent evaporated *in vacuo* to give an off-white solid that was triturated with boiling MeOH to give the title compound as a white solid (210mg, 49%). δ H (DMSO- d_6) 11.18 (1H, br s, CO₂H), 10.66 (1H, s, NH), 8.89 (1H, d, \downarrow 8.0Hz), 8.30 (1H, dd, \downarrow 1.6, 4.7Hz), 7.77 (1H, dd, \downarrow 1.6, 7.6Hz), 7.62-7.45 (5H, m), 7.32 (2H, d, \downarrow 8.5Hz), 7.17 (1H, dd, \downarrow 4.8, 7.6Hz), 6.96 (3H, m), 4.62 (1H, m), 3.70 (3H, s), 3.60 (3H, s) and 3.20-3.00 (2H, m). m/z (ES⁺) 626,628 (MH⁺).

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35

The following compounds were prepared in a similar manner to the compound of Example 4a) by hydrolysis of the corresponding methyl ester. Each ester was obtained by coupling the starting materials shown according to the method described for Intermediate 6:

a) **2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine**

from (N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester and 3,5-dichloropyridyl-4-carbonyl chloride. δ H (DMSO- d_6) 8.64 (2H, s), 7.60-7.46 (5H, m), 7.24 (2H, d, \downarrow 8.5Hz), 4.78-4.65 (1H, m), 3.22-2.85 (2H, m); δ H m/z (ESI, 60V) 528 (MH⁺).

c) **(N'-2,4-Dimethylnicotinoyl)-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine**

from (N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester and 2,4-dimethylpyridyl-4-carbonyl chloride. δ H (DMSO- d_6) 8.39 (1H, br d), 8.23 (1H, d, \downarrow 5.0Hz), 7.59-7.45 (6H, m), 7.26 (2H, d, \downarrow 8.4Hz), 7.01 (1H, d, \downarrow 5.1Hz), 4.65-4.52 (1H, m), 3.26-3.18 (1H, m), 2.95-2.84 (1H, m), 2.17 (3H, s), 2.01 (3H, s); m/z (ESI, 60V) 486 (MH⁺).

d) **N-(2,6-Dichloroisonicotinoyl)-O-(2,6-dichlorobenzyl)-L-tyrosine**

from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2,6-dichloropyridyl-4-carbonyl chloride. δ H (DMSO- d_6) 9.2 (1H, d), 7.81 (2H, s), 7.5-7.3 (3H, m), 7.21 (2H, d, \downarrow 8.5Hz), 6.93 (2H, d, \downarrow 8.5Hz), 5.15 (2H, s), 4.65 (1H, m), 3.28-3.15 (1H, m), 3.05-2.95 (1H, m); m/z (ESI, 60V) 513 (MH⁺).

e) **N'-(2-nicotinoyl)-O-(2,6-dichlorobenzyl)-L-tyrosine**

from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and nicotinoyl chloride using triethylamine as base. δ H (DMSO- d_6) 9.0-8.85 (2H, m), 8.7 (1H, m), 8.14 (1H, m), 7.55-7.41 (4H, m), 7.24 (2H, d, \downarrow 8.6Hz), 6.95 (2H, d, \downarrow 8.6Hz), 5.16 (2H, s), 4.59 (1H, m), 3.17-3.12 (1H, m), 3.04-2.96 (1H, m); m/z (ESI, 60V) 445 (MH⁺).

f) **N-(3,5-Dichloro-4-picolyl)-N'-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine**

from (N-3,5-dichloro-4-picolyl)-L-4-aminophenylalanine methyl ester and 3,5-dichlorophthalidyl-4-carbonyl chloride. δ H (DMSO- d_6 , 300MHz) 9.26 (1H, d, J 8.3Hz), 8.79 (2H, s), 8.65 (2H, s), 7.57 (2H, d, J 8.4Hz), 7.30 (2H, d, J 8.4Hz), 4.70 (1H, m), 3.15 (1H, dd, J 14.1, 5.2Hz) and 2.93 (1H, dd, J 14.0, 9.3Hz); m/z (ESI, 160V) 527 (MH⁺).

g) **N-(2-Chloronicotinoyl)-N'-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine**

from (N-3,5-dichloro-4-picolyl)-L-4-aminophenylalanine methyl ester and 2-chloro-nicotinoyl chloride. δ H (DMSO- d_6 , 300MHz) 12.85 (1H, br s), 10.88 (1H, s), 8.97 (1H, d, J 8.1Hz), 8.79 (2H, s), 8.46 (1H, dd, J 4.8, 1.8Hz), 7.70 (1H, dd, J 7.5, 1.8Hz), 7.59 (2H, d, J 8.4Hz), 7.48 (1H, dd, J 7.5, 4.8Hz), 7.30 (2H, d, J 8.4Hz), 4.63 (1H, m), 3.16 (1H, dd, J 13.9, 4.7Hz) and 2.95 (1H, dd, J 13.8, 9.8Hz) m/z (ESI, 160V) 493 (MH⁺).

EXAMPLE 5

a) **O-(2,6-dichlorobenzyl)-N-(4-acetyl-1,2,5-trimethyl-3-pyrrolyl)-L-tyrosine**

Intermediate 7 (360mg, 0.68mmol) was treated with LiOH.H₂O (34mg, 0.81mmol) in dioxane (6ml), water (6ml) and MeOH (4ml) at room temperature for 2h. The solvent was removed *in vacuo* and the obtained residue taken up in water. The pH was made acidic by addition of a few drops of acetic acid and the obtained precipitate filtered off with water washing affording the title compound as a white amorphous powder (245mg, 70%). δ H (d_6 -DMSO) 8.37 (1H, d, J 8.2Hz, NH), 7.57-7.43 (3H, m's, aryl-H), 7.23 (2H, d, J 8.6Hz, aryl-H), 6.95 (2H, d, J 8.6Hz, aryl-H), 5.18 (2H, br s, CH₂-O), 4.62 (1H, m, α tyr-H), 3.33 (3H, s, MeN), 3.13 (1H, dd, J 4.1, 13.8Hz, CH_AH_BAr), 2.32 (3H, s, MeCO), 2.01 (3H, s, pyrrole-Me) and 1.92 (3H, s, pyrrole-Me). m/z (ES⁺, 60V), 517 (MH⁺, 100), 519 (MH⁺, 70).

The following compounds were prepared in a similar manner to the compound of Example 5a) by hydrolysis of the corresponding methyl ester.

Each ester was obtained by coupling the starting materials shown according to the method described for Intermediate 7:

b) **O-(2,6-dichlorobenzyl)-N-(4-acetyl-3,5-dimethyl-2-pyrrolyl)-L-tyrosine**

5 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 3,5-dimethyl-4-acetylpyrrole-2-carboxylic acid. Freeze drying afforded the title compound as a light cream amorphous solid (550mg). δ H (DMSO- d_6) 11.56, (1H, s), 7.61 (1H, d, J 7.8Hz), 7.51 (2H, d, J 8.0Hz), 7.41 (1H, t, J 8.0Hz), 7.21 (2H, d, J 8.5Hz), 6.96 (2H, d, J 8.5Hz), 5.16 (2H, s), 4.69-4.55
10 (1H, m), 3.12 (1H, dd, J 13.7, 4.7Hz), 2.99 (1H, dd, J 13.7, 9.1Hz), 2.43 (3H, s), 2.38 (3H, s), 2.31 (3H, s); m/z (ESI, 60V) 503 (MH⁺).

c) **O-(2,6-dichlorobenzyl)-N-(4-acetyl-2,5-dimethyl-3-pyrrolyl)-L-tyrosine**

15 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2,5-dimethyl-4-acetylpyrrole-3-carboxylic acid. Freeze drying afforded the title compound as a white amorphous solid (203mg). δ H (DMSO- d_6) 11.2 (1H, s), 8.83 (1H, d, J 8.0Hz), 7.56 (2H, app.d, J 8.0Hz), 7.45 (1H, app.t, J 8.0Hz), 7.21 (2H, d, J 8.5Hz), 6.95 (2H, d, J 8.5Hz), 5.17 (2H, s), 4.61-4.52
20 (1H, m), 3.11 (1H, dd, J 13.8, 4.3Hz), 2.86 (1H, dd, J 13.8, 10.4Hz), 2.31 (3H, s), 2.08 (3H, s), 2.07 (3H, s); m/z (ESI, 60V) 503 and 505 (MH⁺).

d) **O-(2,6-dichlorobenzyl)-N-(1-methyl-2-indolyl)-L-tyrosine**

25 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 1-methylindole-2-carboxylic acid. Freeze drying afforded the title compound as a white amorphous solid (220mg). δ H (DMSO- d_6) 11.7 (1H, br s), 8.66 (1H, d, J 8.3Hz), 7.65 (1H, d, J 7.9Hz), 7.53 (2H, app.d, J 8.1Hz), 7.26 (1H, obscured m), 7.09 (2H, app.t, J 7.5Hz), 6.96 (2H, d, J 8.5Hz), 5.16
30 (2H, s), 4.64-4.54 (1H, m), 3.89 (3H, s), 3.16 (1H, dd, J 13.8, 4.3Hz) and 3.00 (1H, dd, J 13.8, 10.4Hz); m/z (ESI, 60V) 497 and 499 (MH⁺).

e) **O-(2,6-dichlorobenzyl)-N-[2-(4-chlorophenyl)-3-(trifluoromethyl)-4-pyrazoyl]-L-tyrosine**

35 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2-(4-chlorophenyl)-3-(trifluoromethyl)-pyrazole-4-carboxylic acid. The title

compound was isolated as an off-white solid (220mg). δ H (DMSO- d_6) 11.17 (1H, br s), 8.82 (1H, d, \downarrow 8.2Hz), 8.08 (1H, s), 7.65 (2H, d, \downarrow 8.1Hz), 7.54 (4H, app. d, \downarrow 8.1Hz), 7.45 (1H, app. t, \downarrow 8.0Hz), 7.24 (2H, d, \downarrow 8.3Hz), 6.98 (2H, d, \downarrow 8.3Hz), 5.18 (2H, s), 4.61-4.51 (1H, m), 3.17 (1H, dd, \downarrow 13.8, 4.5Hz) and 2.94 (1H, dd, \downarrow 13.8, 9.0Hz); m/z (ESI, 60V) 527 and 529 (MH⁺).

f) **O-(2,6-dichlorobenzyl)-N-(2-phenyl-4-thiazoyl)-L-tyrosine**
from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2-phenyl-thiazole-4-carboxylic acid. Freeze-drying afforded the title compound as a pale yellow amorphous solid (340mg). δ H (DMSO- d_6) 11.2 (1H, br s), 8.40 (1H, d, \downarrow 8.1Hz), 8.31 (1H, s), 8.05-8.02 (2H, m), 7.55-7.51 (5H, m), 7.46-7.40 (1H, m), 7.23 (2H, d, \downarrow 8.0Hz), 6.97 (2H, d, \downarrow 7.8Hz), 5.16 (2H, s), 4.71-4.64 (1H, m), 3.18 (2H, app. d, \downarrow 6.6Hz); m/z (ESI, 60V) 527 and 529 (MH⁺).

g) **(N'-1-Methyl-5-nitropyrzoyl)-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine**
from (N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester with N-methyl-5-nitropyrzole-4-carboxylic acid. δ H (DMSO- d_6) 10.64-(1H, s), 8.68 (1H, br d), 7.80 91H, s), 7.64-7.48 (6H, m), 7.19 (2H, d, \downarrow 8.5Hz), 4.59-4.49 (1H, m), 4.05 (3H, s), 3.18-2.9 (2H, m); m/z (ESI, 60V) 506 (MH⁺).

h) **N-(2-Methylnicotinoyl)-O-(2,6-dichlorobenzyl) L-tyrosine**
from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2-methylnicotinic acid. δ H (DMSO- d_6) 8.73 (1H, br d), 8.48 (1H, m), 7.7-7.46 (4H, m), 7.4-7.23 (3H, m), 7.00 (2H, d, \downarrow 8.4Hz), 5.2) (2H, s), 4.60 91H, m), 3.27-3.12 (1H, m), 3.0-2.82 (1H, m); m/z (ESI, 60V) 509 (MH⁺).

i) **(N'-2-Chloronicotinoyl)-(N-benzoyl)-L-4-aminophenylalanine**
from (N-benzoyl)-L-4-aminophenylalanine methyl ester and 2-chloronicotinic acid. δ H (DMSO- d_6) 10.19 (1H, s), 8.96 (1H, d, \downarrow 8.2Hz), 8.46 (1H, dd, \downarrow 4.8, 1.9Hz), 7.96 (2H, dd, \downarrow 6.7, 1.7H), 7.75-7.65 (3H, m), 7.62-7.45 (4H, m), 7.25 (2H, d, \downarrow 8.5Hz), 4.6 (1H, m), 3.2-3.12 (1H, m), 3.0-2.89 (1H, m), m/z (ESI, 60V) 424 (MH⁺).

- j) **N'-(Quinoline-4-carbonyl)-O-(2,6-dichlorobenzyl)-L-tyrosine**
 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochlorid and 4-quinoline carboxylic acid. δ H (DMSO- d_6) 9.0 (1H, d), 8.94 (1H, d, \downarrow 4.3),
 5 8.06 (1H, d, \downarrow 8.2Hz), 7.79 (2H, m), 7.62-7.42 (4H, m), 7.34 (1H, d, \downarrow 4.3Hz), 7.34 (2H, d, \downarrow 8.7Hz), 7.00 (2H, d, \downarrow 8.7Hz), 5.22 (2H, s), 4.72 (1H, m), 3.29-3.19 (1H, m), 3.0-2.88 (1H, m); m/z (ESI, 60V) 495 (MH⁺).
- k) **N'-(2-Phenoxynicotinoyl)-O-(2,6-dichlorobenzyl)-L-tyrosine**
 10 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2-phenoxynicotinic acid. δ H (DMSO- d_6) 8.55 (1H, d), 8.18 (2H, m), 7.6-7.4 (5H, m), 7.3-7.15 (6H, m), 6.71 (2H, d), 5.1 (2H, s), 4.65 (1H, m), 3.22-3.0 (2H, m); m/z (ESI, 60V) 537 (MH⁺).
- 15 l) **N-(Pyridine-2-carbonyl)-O-(2,6-dichlorobenzyl)-L-tyrosine**
 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2-picolinic acid. δ H (DMSO- d_6) 8.8-8.6 (2H, m), 8.0 (2H, m), 7.7-7.4 (4H, m), 7.14 (2H, d, \downarrow 8.7Hz), 6.92 (2H, d, \downarrow 8.7Hz), 5.15 (2H, s), 4.72 (1H, m), 3.17 (2H, m); m/z (ESI, 60V) 445 (MH⁺).
- 20 m) **N-(Pyridine-4-carbonyl)-O-(2,6-dichlorobenzyl)-L-tyrosine**
 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and isonicotinic acid. δ H (DMSO- d_6) 8.68 (2H, dd, \downarrow 4.5, 1.6Hz), 8.4 (1H, d, \downarrow 7.2Hz), 7.63 (2H, dd, \downarrow 4.5, 1.6Hz), 7.6-7.4 (3H, m), 7.15 (2H, d, \downarrow 8.6Hz),
 25 6.87 (2H, d, \downarrow 8.6Hz), 5.14 (2H, s), 4.31 (1H, m), 3.2-2.96 (2H, m); m/z (ESI, 60V) 445 (MH⁺).
- n) **N-(2-Hydroxynicotinoyl)-O-(2,6-dichlorobenzyl)-L-tyrosine**
 from O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride and 2-hydroxynicotinic acid. δ H (DMSO- d_6) 10.15 (1H, d, \downarrow 7.4Hz), 8.31 (1H, dd, \downarrow 7.1, 2.0Hz), 7.71 (1H, br s), 7.65-7.45 (3H, m), 7.16 (2H, d, \downarrow 8.4Hz), 6.97 (2H, d, \downarrow 8.4Hz), 6.46 (1H, t, \downarrow 6.8Hz), 5.17 (2H, s), 4.68 (1H, m), 3.2-3.0 (2H, m); m/z (ESI, 60V) 461 (MH⁺).
- 35) **(N'-2-Aminonicotinoyl)-(N-2,6-dichlorobenzoyl)-L-4-amino phenylalanine**

from (N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester and 2-aminonicotinic acid. δ H (DMSO- d_6) 10.64 (1H, s), 8.55 (1H, d), 8.06 (1H, m), 7.8 (1H, d), 7.7-7.4 (4H, m), 7.28 (2H, d, \downarrow 8.5Hz), 6.9 (2H, br s), 6.5 (1H, m), 4.52 (1H, m), 3.2-2.9 (2H, m); m/z (ESI, 60V) 473 (MH⁺).

5

p) (N'-2-Hydroxynicotinoyl)-(N-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

from (N-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester and 2-hydroxynicotinic acid. δ H (DMSO- d_6) 10.14 (1H, d, \downarrow 7.6Hz), 8.78 (2H, s), 8.31 (1H, dd, \downarrow 7.2, 2.2Hz), 7.70 (1H, br m), 7.57 (2H, d, \downarrow 8.5Hz), 7.20 (2H, d, \downarrow 8.5Hz), 6.46 (1H, m), 4.69 (1H, m), 3.20-2.95 (2H, m); m/z (ESI, 60V) 475 (MH⁺).

10

q) (N'-2-Methylnicotinoyl)-(N-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

from (N-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine and 2-methylnicotinic acid. δ H (DMSO- d_6) 8.78 (2H, s), 8.60 (1H, br d), 8.48 (1H, dd, \downarrow 4.8, 1.6Hz), 7.7-7.5 (3H, m), 7.4-7.2 (3H, m), 4.5 (1H,), 3.3-2.85 (2H, m), 2.34 (3H, s); m/z (ESI, 60V) 473 (MH⁺).

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r) (N'-2,6-Dichlorobenzoyl)-(N-2-phenoxy nicotinoyl)-L-4-aminophenylalanine

from (N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester and 2-phenoxy nicotinic acid. δ H (DMSO- d_6) 10.61 (1H, s), 8.56 (1H, d, \downarrow 7.5Hz), 8.22-8.17 (2H, m), 7.59-7.39 (8H, m), 7.27-7.11 (7H, m), 4.72-4.64 (1H, m, CH), 3.16 (1H, dd, \downarrow 13.7, 4.9Hz, CH_AH_B) and 3.06 (1H, dd, \downarrow 13.7, 7.8Hz, CH_AH_B); m/z (ESI, 60V) 550 (MH⁺).

25

s) (N-3,5-Dichloroisonicotinoyl)-(N-2-phenoxy nicotinoyl)-L-4-aminophenylalanine

from (N-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester and 2-phenoxy nicotinic acid. δ H (DMSO- d_6) 10.79 (1H, s), 8.78 (2H, s, ArH), 8.57 (1H, d, \downarrow 7.6Hz), 8.25-8.13 (2H, m), 7.46-7.35 (4H, m), 7.29-7.05 (6H, m), 4.73-4.62 (1H, m, CH), 3.17 (1H, dd, \downarrow 13.7, 4.7Hz, CH_AH_B) and 3.09 (1H, dd, \downarrow 13.7, 7.8Hz, CH_AH_B); m/z (ESI, 60V) 551 (MH⁺).

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35

t) ***N*-(4-Acetyl-1,2,5-trimethyl-1*H*-pyrrol-3-carbonyl)-*N'*-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine**

from (N-3,5-dichloro-4-picolyl)-L-4-aminophenylalanine methyl ester and 4-acetyl-1,2,5-trimethyl-1*H*-pyrrole-3-carboxylic acid. δ H (DMSO- d_6 , 300MHz) 400K) 12.72 (1H, br s), 10.83 (1H, s), 8.80 (2H, s), 8.42 (1H, d, \downarrow 8.4Hz), 7.54 (2H, d, \downarrow 8.5Hz), 7.30 (2H, d, \downarrow 8.4Hz), 4.66 (1H, m), 3.34 (3H, s), 3.16 (1H, dd, \downarrow 13.8, 4.3Hz), 2.89 (1H, dd, \downarrow 13.8, 11.0Hz), 2.32 (3H, s), 2.05 (3H, s) and 1.90 (3H, s); m/z (ESI, 60V) 531 (MH⁺).

u) ***N*-(4-(Carboxy)nicotinoyl)-*N'*-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine**

from (N-3,5-dichloro-4-picolyl)-L-4-aminophenylalanine methyl ester and 4-(methoxycarbonyl)nicotinic acid. δ H (DMSO- d_6 , 300MHz) 10.98 (1H, s), 9.01 (1H, d, \downarrow 8.0Hz), 8.77 (2H, s), 8.63 (1H, s), 7.66 (1H, d, \downarrow 5.1Hz), 7.59 (2H, d, \downarrow 8.5Hz), 7.32 (2H, d, \downarrow 8.5Hz), 4.63 (1H, m), 3.14 (1H, dd, \downarrow 13.9, 5.4Hz) and 3.03 (1H, dd, \downarrow 13.9, 8.8Hz); m/z (ESI, 160V) 503 (MH⁺).

v) **(2-Acetyl-3-thienyl)carbonyl-(*N*-3,5-dichloro-4-picolyl)-L-4-aminophenylalanine**

from (N-3,5-dichloro-4-picolyl)-L-4-aminophenylalanine methyl ester and 2-acetyl-thiophene-3-carboxylic acid. δ H (DMSO- d_6) 9.17 (1H, d, \downarrow 8.2Hz, NH), 8.77 (2H, s, pyr-H), 7.99 (1H, d, \downarrow 5.1Hz, thiophene H-5), 7.57 (2H, ABd, \downarrow 8.5Hz, Ar-H), 7.31 (2H, ABd, 2H, \downarrow 8.5Hz, Ar-H), 7.07 (1H, d, \downarrow 5.1Hz, thiophene H-4), 5.38 (1H, m, CH α) 3.18 (1H, dd, \downarrow 13.8, 4.6Hz, CHCH_AH_BAr), 2.93 (1H, dd, \downarrow 13.8, 10.3Hz, CHCH_AH_BAr) and 2.26 (3H, s, COMe); m/z (ESI, 60V) 506 (MH⁺).

EXAMPLE 6

a) **2-Chloronicotinoyl-(*N*-2,6-dichlorobenzoyl)-L-4-aminophenylalanine**

Lithium hydroxide monohydrate (109mg, 2.5mmol) was added to a solution of Intermediate 8 (450mg, 1mmol) in a mixture of THF (10ml) and water (10ml). The mixture was stirred for 2h at room temperature, then the THF was evaporated *in vacuo*. The aqueous residue was neutralised (1M hydrochloric acid), and the precipitate isolated by filtration, washed with water and dried to give the title compound (300mg, 61%). δ H (DMSO- d_6 ,

400K) 8.90 (1H, d, \downarrow 9.1Hzm 1NH), 8.48 (1H, m, Py H), 7.69 (1H, m, Py H), 7.64-7.45 (7H, m, 4ArH, 1 NH, 1 PyH), 7.29 (2H, d, \downarrow 8.3Hz, 2 ArH), 4.66-4.53 (1H, m, CH α tyr), 3.18 (1H, dd, \downarrow 14, 5.2Hz CH_AH_BAr), and 2.91 (1H, dd, \downarrow 9.6, 14Hz, CH_AH_BAr). m/z (ESI, 60V) 491 (MH⁺).

5

The following compounds were prepared in a similar manner:

b) N-(2-Chloronicotinoyl)-O-(2,6-dichlorobenzoyl)-L-tyrosine

from Intermediate 30 to give the title compound as a white solid. δ H

10 (DMSO- d_6 , 300MHz) 12.91 (1H, br s, CO₂H), 8.98 (1H, d, \downarrow 8.3Hz, CONH), 8.44 (1H, dd, \downarrow 4.8, 1.9Hz, PyH), 7.69-7.58 (4H, m, Cl₂ArH₃ + PyH), 7.45 (1H, dd, \downarrow 7.5, 4.9Hz, PyH), 7.43 (2H, d, \downarrow 8.7Hz, ArH), 7.22 (2H, d, \downarrow 8.5Hz, ArH), 4.67 (1H, ddd, \downarrow 10.0, 8.2, 4.7Hz, CH α), 3.24 (1H, dd, \downarrow 14.0, 4.0Hz, CH_AH_BAr) and 2.99 (1H, dd, \downarrow 13.9, 10.2Hz, CH_AH_BAr);
15 m/z (ESI, 60V) 493 (MH⁺).

c) N-(2-Chloronicotinoyl)-N-methyl-N'-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine

from Intermediate 31 to give the title compound as a white solid δ H

20 (DMSO- d_6 , 300MHz, 405K) 10.36 (1H, br s, CONH), 8.67 (2H, s, Cl₂PyH), 8.42-8.39 (1H, m, ClPyH), 7.54-7.15 (6H, br m, 4 x ArH + 2 x ClPyH), 5.30 (1H, v br s, CH α), 3.4-2.6 (5H, br m, NMe + CHCH₂Ar) (Acid proton not observed at 405K, at 300K δ H 13.06 (1H, br s, CO₂H)); m/z (ESI, 70V) 507 (MH⁺).

25 d) [(S-2,5-dimethoxyphenyl)sulphonyl]nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine

from Intermediate 32 δ H (DMSO- d_6) 8.57 (2H, m, pyrH, NH), 7.83 (1H, d, \downarrow 7.8Hz, pyr-H), 7.69 (1H, dd, \downarrow 7.8, 4.7Hz, pyr-H), 7.55 (4H, m, Ar-H), 7.28-7.22 (3H, m, Ar-H), 7.07 (1H, d, \downarrow 9.1Hz, Ar-H), 6.95 (2H, d, \downarrow 8.5Hz, Ar-H), 5.18 (1H, s, CH₂O), 4.55 (1H, m, CH α), 3.81 (3H, s, OMe), 3.40 (3H, s, OMe) and 3.07 (2H, m, CHCH₂Ar). m/z (ESI, 30V) 645 (MH⁺).

30

e) 2-[(2-Chloro-3-pyridinyl)carbonylamino]-3-(4-[(2,6-dichloroanilino)carbonyl]phenyl)propanoic acid

from Intermediate 15 to give the title compound as an off white solid δ H (DMSO- d_6 , 300K) 11.06 (1H, br s), 10.23 (1H, br s), 9.00 (1H, d, \downarrow 7.8Hz), 8.46 (1H, br d), 7.95 (2H, d, \downarrow 7.4Hz), 7.69 (1H, d, \downarrow 7.1Hz), 7.59 (2H, d, \downarrow 8.0Hz), 7.50-7.36 (3H, m), 4.71 (1H, br), 3.26 (1H) and 3.06 (1H, dd, \downarrow 13.8, 10.0Hz); m/z (ESI, 60V) 492 (MH⁺).

f) 2-[(2-Chloro-3-pyridinyl)carbonyl]amino-3-(4-[(3,5-dichloro-4-pyridinyl)amino]carbonyl)phenyl propionic acid

from the corresponding intermediate ester prepared in a similar way to Intermediate 15 to give title compounds as an offwhite solid. δ H (DMSO- d_6 , 300MHz) 12.92 (1H, br s), 10.57 (1H, s), 9.00 (1H, d, \downarrow 8.2Hz), 8.75 (2H, s), 8.45 (1H, dd, \downarrow 4.7, 1.7Hz), 7.96 (2H, d, \downarrow 8.15Hz), 7.69 (1H, d, \downarrow 7.3, 1.7Hz), 7.49 (2H, d, \downarrow 8.0Hz), 7.48 (1H, 4.71 (1H, br m), 3.28 (1H, dd, \downarrow 13.9, 4.7Hz) and 3.06 (1H, dd, \downarrow 13.9, 10.0Hz); m/z (ESI, 60V) 483 (MH⁺).

EXAMPLE 7

2-Thio(S-acetic acid)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine

Lithium hydroxide monohydrate (75mg, 1.8mmol) was added to a solution of Intermediate 9 (360mg, 0.6mmol) in a mixture of THF (13ml) and water (10ml). The mixture was stirred for 2hr at room temperature, then the THF was evaporated *in vacuo*. The aqueous residue was neutralised (1M hydrochloric acid), and the precipitate isolated by filtration, washed with water and dried to give the title compound (200mg, 58%). δ H (DMSO- d_6 , 400K), 8.5-8.35 (2H, m, pyrH, 1NH), 7.71 (1H, dd, \downarrow 1.7, 7.6, pyrH), 7.57 (2H, d, \downarrow 8.9, 2ArH), 7.45 (1H, m, 1ArH), 7.22 (2H, d, \downarrow 8.5, 2ArH), 7.18 (1H, m, 1pyrH), 6.97 (2H, d, \downarrow 8.5, 2ArH), 5.18 (2H, s, OCH₂Ar), 4.43 (1H, m, CH α tyr), 3.82 (2H, s, SCH₂CO₂H), 2.94-3.23 (2H, m, CH₂Ar); m/z (ESI, GOU) 535 (MH⁺).

EXAMPLE 8

2-Thio(S-methyl)nicotinoyl-O-(2,6-dichlorobenzyl)-L-tyrosine

Lithium hydroxide monohydrate (140mg, 3.3mmol) was added to a solution of Intermediate 10 (1.4gm, 2.7mmol) in a mixture of THF (10ml) and water (10ml). The mixture was stirred for 2 hr at room temperature then the THF was vaporat d *in vacuo*. Th aqua ous residu was neutralised (1M

hydrochloric acid), and the precipitate isolated by filtration, washed with water and dried to give the title compound (1.1gm, 81%). δ H (DMSO- d_6 , 400K) 8.73 (1H, d, \downarrow 8.1, NH), 8.52 (1H, dd, \downarrow 1.7, 4.8, 1pyrH), 7.67 (1H, dd, \downarrow 1.7, 7.6, 1pyrH), 7.55 (2H, d, \downarrow 8.9, 2ArH), 7.45 (1H, dd, \downarrow 2.3, 8.9, 1ArH), 7.24 (2H, d, \downarrow 8.6, 2ArH), 7.16 (1H, m, 1pyrH), 6.99 (2H, d, \downarrow 8.6, 2ArH), 5.18 (2H, s, OCH₂Ar), 4.55 (1H, m, CH₂tyr), 3.16-2.95 (2H, m, CH₂Ar) and 2.38 (3H, s, SCH₃); m/z (ESI, GOU) 491 (MH⁺).

EXAMPLE 9

(N-2-Chloronicotinoyl)-4-[(E)-2-(2,6-dichlorophenyl)ethenyl]phenylalanine

To a solution of Intermediate 28 (1.0g, 1.99mmol) in THF (5ml) and water (5ml) was added lithium hydroxide monohydrate (88mg 2.09mmol). The reaction mixture was stirred for 1h. The THF was then removed *in vacuo* and the remaining aqueous solution acidified to pH6 with 1M hydrochloric acid. The resulting precipitate was collected and washed with water and ether and finally freeze dried. The resulting compound contained an impurity so a small amount was purified by preparative HPLC (98mg). δ H (DMSO- d_6) 12.90 (1H, dr s, CO₂H), 8.98 (1H, d, \downarrow 8.0Hz), 8.45 (1H, d, \downarrow 3.4Hz), 7.70-7.03 (9H, m), 4.72-4.60 (1H, m, CH), 3.20 (1H, dd, \downarrow 14.0, 4.5Hz, CH_AH_B) and 3.01 (1H, dd, \downarrow 14.0, 9.9Hz, CH_AH_B); m/z (ESI, 60V) 475 (MH⁺).

EXAMPLE 10

(N-2-Chloronicotinoyl)-4-[2-(2,6-dichlorophenyl)-2-hydroxyethyl]phenylalanine

Lithium hydroxide monohydrate (13mg) was added to a solution of Intermediate 22 (150mg, 0.29mmol) in THF (5ml) and H₂O (5ml). The solution was stirred for 1h and then the THF removed *in vacuo* and the remaining aqueous solution acidified to pH6 with 1M hydrochloric acid. The solid precipitate formed was collected by filtration, washed with copious quantities of water and finally freeze dried to give the title compound as a fluffy white solid (70mg, 49%). δ H (DMSO- d_6) 12.78 (1H, br s, CO₂H), 8.90 (1H, d, \downarrow 8.0Hz), 8.45 (1H, d, \downarrow 4.8Hz), 7.63-7.58 (1H, m, ArH), 7.49-7.45 (1H, m, ArH), 7.34-7.07 (7H, m, ArH), 5.50-5.45 (1H, m,

CH), 4.61-4.51 (1H, m, CH) and 3.30-2.35 (4H, m, 2 x CH₂); m/z (ESI, 60V) 493 (MH⁺).

EXAMPLE 11

5 (N-2-Chloronicotinoyl)-{4-[2-(2-dichlorophenyl)-2-oxoethyl]} phenylalanine

Lithium hydroxide monohydrate (36mg, 0.85mmol) was added to a solution of Intermediate 23 (400mg, 0.77mmol) in THF (5ml) and water (5ml). The reaction mixture was stirred for 3h and then the THF was removed *in vacuo*. The remaining aqueous solution was acidified with 1M hydrochloric acid. The resulting white precipitate was collected and washed well with water. Further purification by column chromatography (SiO₂; acetic acid: MeOH:DCM, 2:8:90) gave the title compound as a white solid (78mg, 19%). δ H (DMSO-d₆) 8.45 (1H, dd, \downarrow 4.8, 2.0Hz), 8.03 (1H, dd, \downarrow 7.7, 2.0Hz), 7.36-7.20 (8H, m, ArH), 6.98 (1H, d, \downarrow 7.2Hz, ArH), 5.14-5.05 (1H, m, CH), 4.11 (2H, s, CH₂C=O)m, 3.39 (1H, dd, \downarrow 14.1, 5.6Hz, CH_AH_B) and 3.25 (1H, dd, \downarrow 14.1, 6.2Hz, CH_AH_B); m/z (ESI, 60V) 491 (MH⁺).

20 $\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with F(ab)₂ fragment goat anti-human IgG Fc γ -specific antibody [Jackson Immuno Research 109-006-098: 100 μ l at 2 μ g/ml in 0.1M NaHCO₃, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 μ l containing 2.5 x 10⁵ Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100 μ l methanol for 10 minutes followed by another wash. 100 μ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100 μ l 50% (v/v)

ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

- 5 This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β -lymphoblastoid cell-line JY was used in place of Jurkat cells. The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

10

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

- 96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 μ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 15 100 μ l PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200 μ l containing 2.5x 10⁵ K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed 20 and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic

- 96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h 25 at 37°C. 2 x 10⁵ freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 μ l in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 30 100 μ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H₂O₂ 35 (Sigma) and 50 μ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

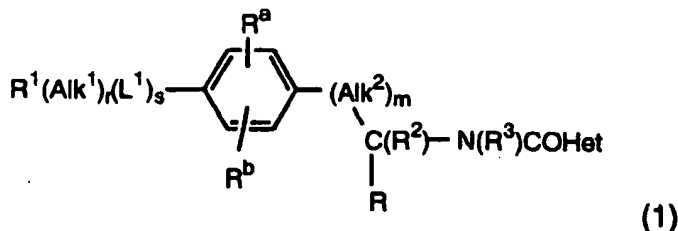
α IIb/ β ₃-dependent human platelet aggregation

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6×10^8 /ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; MgCl₂.H₂O 0.427; CaCl₂ 0.2; KCl 0.2; D-glucose 1.0; NaHCO₃ 1.0; NaHPO₄.2H₂O 0.065). Aggregation was monitored following addition of 2.5 μ M ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the compounds of the invention generally have IC₅₀ values in the α ₄ β ₁ and α ₄ β ₇ assays of 1 μ M and below. Thus compounds of the Examples typically had IC₅₀ values of 100nM and below in these assays and demonstrated selective inhibition of α ₄ β ₁. In the other assays featuring α integrins of other subgroups the same compounds had IC₅₀ values of 50 μ M and above thus demonstrating the potency and selectivity of their action against α ₄ integrins.

CLAIMS

1. A compound of formula (1)



wherein

R is a carboxylic acid or a derivative thereof;

R¹ is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

L¹ is a linker atom or group;

r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R¹ is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

R^a and R^b, which may be the same or different is each an atom or group -L²(CH₂)_pL³(R^c)_q in which L² and L³ is each a covalent bond or a linker atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^c is a hydrogen or halogen atom or a group selected from straight or branched alkyl, -OR^d [where R^d is a hydrogen atom or an optionally substituted straight or branched alkyl group], -SR^d, -NR^dR^e, [where R^e is as just defined for R^d and may be the same or different], -NO₂, -CN, -CO₂R^d, -SO₃H, -SO₂R^d, -OCO₂R^d, -CONR^dR^e, -OCONR^dR^e, -CSNR^dR^e, -COR^d, -N(R^d)COR^e, N(R^d)CSR^e, -SO₂N(R^d)(R^e), -N(R^d)SO₂R^e, -N(R^d)CONR^eR^f [where R^f is a hydrogen atom or an optionally substituted straight or branched alkyl group], -N(R^d)CSNR^eR^f or -N(R^d)SO₂NR^eR^f;

Alk² is a straight or branched alkylene chain;

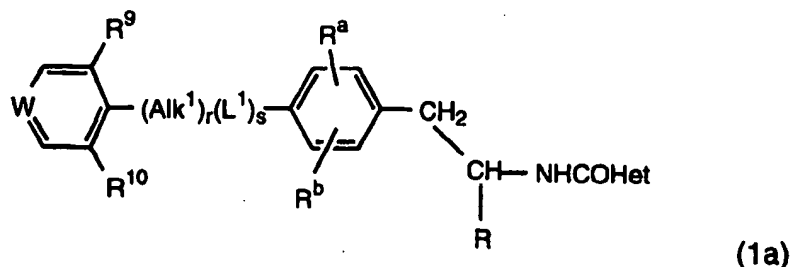
m is zero or an integer 1;

R² is a hydrogen atom or a methyl group;

R³ is a hydrogen atom or a straight or branched alkyl group;

Het is an optionally substituted heteroaromatic group;
and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein Het is an optionally
5 substituted C₃₋₅ monocyclic heteroaromatic group containing one, two or
three heteroatoms selected from oxygen, sulphur or nitrogen atoms.
3. A compound according to Claim 2 wherein Het is an optionally
substituted pyrrolyl or pyridyl group.
10
4. A compound according to any one of Claim 1 to Claim 3 wherein R
is a -CO₂H group.
5. A compound according to any of Claim 1 to Claim 4 wherein Alk² is
15 a -CH₂- chain and is an integer 1.
6. A compound according to any of Claim 1 to Claim 5 wherein each of
R² and R³ is a hydrogen atom.
- 20 7. A compound according to any one of Claim 1 to Claim 6 wherein R¹
is an optionally substituted aromatic or heteroaromatic group.
8. A compound according to Claim 7 wherein R¹ is an optionally
substituted phenyl, pyridyl or pyrimidinyl group.
25
9. A compound according to any one of the preceding claims wherein
-(Alk¹)_r(L¹)_s is a -CH₂O-, -SO₂NH-, -C(O)O- or -CON(R⁴)- group.
10. A compound according to Claim 9 wherein -(Alk¹)_r(L¹)_s is a
30 -CONH- group.
11. A compound of formula (1a):



wherein -W= is -CH= or -N=, R^9 and R^{10} , which may be the same or different is each a $-L^2(CH_2)_pL^3(R^c)_q$ atom or group as generally and particularly defined above, and Alk^1 , r , L^1 , s , R^a , R^b , R and Het are as generally and particularly defined above, and the salts, solvates, hydrates and N-oxides thereof.

12. A compound according to Claim 11 wherein Het is an optionally substituted pyrrolyl or pyridyl group.

13. A compound which is:

2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine;

15 2-Thio(S-2,5-dimethoxyphenyl)nicotinoyl-(N-2,6-dichlorobenzoyl)-L-4-aminophenylalanine;

N-(3,5-Dichloro-4-picolyl)-N'-(3,5-dichloro-4-picolyl)-L-4-amino-phenylalanine;

N-(2-Chloronicotinoyl)-N'-(3,5-dichloro-4-picolyl)-L-4-amino-phenylalanine;

20 O-(2,6-dichlorobenzyl)-N-(4-acetyl-1,2,5-trimethyl-3-pyrrolyl)-L-tyrosine;
(N'-3,5-Dichloroisonicotinoyl)-N-([3-pyridinylmethyl]thio)isonicotinoyl)-L-4-aminophenylalanine;

25 N-(4-Acetyl-1,2,5-trimethyl-1H-pyrrole-3-carbonyl)-N'-(3,5-dichloro-4-picolyl)-L-4-aminophenylalanine; and the salts, solvates, hydrates and N-oxides thereof.

14. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00279

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/82 C07D213/81 C07D207/40 C07D209/42 C07D241/24
C07D277/56 C07D231/14 C07D215/50 C07D401/12 C07D409/12
A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 10312 A (HOFFMANN LA ROCHE) 4 March 1999 see claims; examples	1, 11, 14
X, P	WO 98 53814 A (HAGMANN WILLIAM K ; MUMFORD RICHARD A (US); KEVIN NANCY J (US); MAC) 3 December 1998 see claims; examples	1, 11, 14
X	EP 0 288 176 A (AJINOMOTO KK) 26 October 1988 see compounds S-11 and S-12 see claims	1, 14
A	WO 97 08145 A (DESAI BIPINCHANDRA NANUBHAI ; LINDMARK RICHARD JOHN (US); RUSSELL M) 6 March 1997 see claims 1, 20, 21	1, 14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

11 May 1999

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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